PARASITISM AND DISEASE

LONDON: HUMPHREY MILFORD
OXFORD UNIVERSITY PRESS

E. Worcester Hunt.
Dec '34.

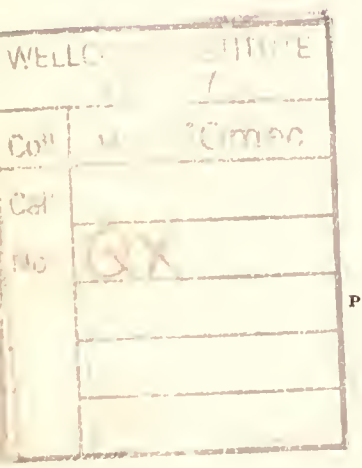
PARASITISM AND DISEASE

By THEOBALD SMITH

Director Emeritus of the Department of Animal Pathology
Rockefeller Institute for Medical Research

PUBLISHED ON THE LOUIS CLARK VANUXEM FOUNDATION

PRINCETON
PRINCETON UNIVERSITY PRESS
1934



PRINTED AT PRINCETON UNIVERSITY PRESS
PRINCETON, NEW JERSEY, U.S.A.

CONTENTS

INTRODUCTION

THE highly diversified topics of the Vanuxem lectures as given in the past and the array of talent responsible for them show that there are no restrictions placed upon the choice of subjects, except perhaps that the choice of lecturers determines the field. It had long been my desire to bring together all alien invaders and parasites of the animal body and deal with them and the disturbances they produce under some unifying principle. Certain efforts of this sort, as in the Lowell lectures in 1909 and the Herter lectures in 1916, were left unpublished. The present series is a final attempt at showing the relation between disease and parasitism in its broadest manifestations. The undertaking has proved more difficult than had been anticipated, partly because of the necessity of mingling indiscriminately everyday knowledge with highly abstruse biological reactions in attempts at illustration, partly because nature refuses to remain long in any theoretical strait-jacket conceived by man. The lectures on which this book is based are, however, a unity in that the same phenomenon, the struggle of man and higher animals against infectious and invasive disease agents, is viewed from the outside and from different angles, for as yet we cannot penetrate to the heart of the phenomenon of life and express it in some complex mathematical formula.

Since there is no clear line to be drawn between the diseases of man and the higher warm-blooded animals, illustrations will be taken from any of these sources available. The time to regard human diseases as something apart closed with the studies of Pasteur and Koch. Today every pathological disturbance in animals is being examined with care to bring to

the surface, if possible, the means to interpret those conditions in human diseases still obscurely understood.

To give a course of lectures on disease to a mixed audience would have been an impossibility, let us say, fifty years ago, partly because there was little or nothing to say. Today, owing to the fact that disease has become a biological problem, that it is ranging itself among natural phenomena in our minds, that it can be interpreted in terms of natural law, and that it can be discussed objectively, it is no longer in the hands of professional mystics.

That we are dealing with a highly complex unit, the living animal, in which every organ stands in some relation to every other organ or tissue makes a certain amount of repetition inevitable. It has, however, the redeeming quality of driving home the best established facts in the host-parasite conflict. It is unfortunate that technical terms cannot be avoided and that they cannot be translated into common language without great loss of time and interruptions to the normal flow of ideas. Even the actual truth must now and then be strained to simplify the presentation.

I have not been unmindful of the fact that these lectures were primarily for the student body not yet conversant with the problems of disease. Some will take up this study in earnest as medical students. Others will perhaps become sanitary engineers, controlling and supervising water supply and sewerage plants, and the conservation of foods. Others will enter agriculture as a life enterprise, where parasitism is most destructive. Still others as laymen will be drawn into the health councils of city, state and nation, as trustees of hospitals and sanatoria. They should know what it is all about when large appropriations go into these enterprises. Some general fundamental guides on matters of disease all of us need. I say disease because that is the positive factor in our lives; health, a negative one, since it means the absence of disease. These

considerations, added to those given, pointed out the way to follow. Instead of taking some narrow, well defined technique or topic and following it minutely into all its ramifications, open as well as blind, I chose to present the problem as outlined.

The great development of experimental science in the study of the phenomena of life has thrown somewhat into the shadow the older comparative method. The latter looks at things in nature, describes and compares them, and deduces from such comparisons certain underlying concepts. The experimental method takes the same phenomenon and tries to check or limit all but one of the activities entering into it so that this one activity can be observed, recorded, measured, and weighed. Obviously the phenomenon has not been entirely elucidated by this process. Even after we review all conceivable manifestations of the natural phenomenon in this way, there still remains the problem of formulating the properties of the whole on the basis of the interacting activities of its parts. And so it happens that if we apprehend or appropriate an idea that is based on definite experimental proof we are apt to let it overshadow other perhaps more inclusive ideas which have not yet been demonstrated or which from the nature of the case cannot be subjected to rigid demonstration. Both methods have their special advantages and disadvantages. The whole must be supplemented by some means for looking beneath the surface and observing the mechanism that controls its activities. The experimental method must not let too many machines get between it and the whole and must find some way of putting the fragment surgically removed for experimental purposes back into the whole. The comparative method is frequently in position to restrain the generalizations deduced from experimental procedures and to keep the experimenter from steering away from the goal, which is an understanding of the totality.

The subject to be presented deals with living things and the observational, comparative method shares equally with the experimental, analytic method the burden of trying to pry into the behavior of two organisms in conflict. Living things, we are learning day by day, have unlimited capacity for variation and adaptation. They are primarily individualistic and in our experiments can be kept unchanged only by strictest adherence to uniform conditions, not only of environment, but of descent. Watching the evolution of our individual fields of work we can plainly see past errors in the acceptance of uniformity where there has been none to speak of.

In the study of disease due to microbic and higher parasites we can see quite distinctly two lines of development, the theoretical trying to dig beneath the observations towards more fundamental concepts embodied in physics and chemistry, and the medical or practical striving towards the surface to bring research into use. Nevertheless many medical men in this endeavor have dug deep and as a result medical science has greatly enriched biology without specially setting out to do it.

It may be said that the half century just closed covered the adventurous and romantic period of searching for living agents of disease. There was no preconceived formula to apply in aid of discovery. It was the naturalist's period as distinguished from the more precise, experimental machine age in which we now find ourselves. But as each age has a scouting line approaching another unexplored field, so today there lies before the scientist the unknown field of disease agents too small to be seen, and almost too small to be accepted as living organisms. Again naturalists' methods are at work, discovering, sorting out, and classifying things that may never be seen. The pathologist has entered the field of the unknowable in which only behavior and changes in be-

havior are accessible to the usual procedures of weighing and measuring. It is needless to state that certain phases of the life cycle of well known visible parasitic invaders are still only vaguely surmised. The work must go on. Science gnaws irregularly away at the lump of the unknown, and the undigested portions are temporarily bridged over by theories. Moreover the face of nature and of civilization is steadily changing and thereby changing the host-parasite relations. That is to say, we must go on so as not to go backward.

All fields of science reaching out into the practical affairs of mankind have been compelled to protect the products of their labor against opposition of various kinds. The practical implications of discoveries in pathology may be very disturbing and the medical profession has been cautious not to promulgate unripe truths. The knowledge of the function of microorganisms has had to fight its way to recognition step by step. The "germ theory of disease" was a newspaper byword a half-century ago. It would be instructive to spend an hour in giving the history of struggles of public health and sanitation with the conflicting interests of commercial organizations, of city fathers, and religious bodies. It matters little to everyday existence whether scientists differ on the status of the universe, whether it is in an expanding or contracting stage, but it does matter whether rabies in dogs is regarded as a mere fit or a fatal disease for man.

We now know definitely that infectious and parasitic diseases cannot develop without the presence of certain known living agents. There can be no tuberculosis without the tubercle bacillus. However, we can carry within us tubercle bacilli without having the disease. The reason is that microbes are hedged about by bodily conditions for and against them. It would be possible so to exaggerate these adjunct conditions as to make it appear that tubercle bacilli were of little or no consequence. I might in fact have framed these lectures differently

and called them the dogma of the germ theory of disease. The truth is that the relation between the tubercle bacillus and the human body is a complex give and take. By exaggerating any one factor we upset the others. This is precisely what may happen in research from time to time and the unbalance must be smoothed out by further inquiry.

This brings us to the customary expectation in our day to hear the latest and the newest in any discussion or lecture. This accords with the speed with which we travel and work. The desire for newness is stimulated by the atmosphere of the daily press. However, the newest is not always the truest nor has it often the importance at first attached to it. The significance of discoveries in science is frequently greatly exaggerated at the start; some shrink to very small proportions later on. No attempt has therefore been made to include a discussion of the most recent, still highly debatable acquisitions within the field covered by the lectures.

When we come in contact or conflict with new facts through actual experience in the home, the workshop, the garden, the field, or the laboratory, we are duly impressed by them. They have become a part of our life. We do not need theories to hold them together for us. In fact we create the theories ourselves. This is true education. When, however, we learn of new facts through reading and the spoken word, we crave for interpretations and theories that bind information into some kind of unity to simplify mental absorption and digestion. I realize that what I shall tell you needs to be vitalized by actual experience. I am therefore anxious to stimulate a continuing interest in the subject rather than to convey some facts now accessible in other ways. In the end the subject is not devoid of suggestions and lessons contributing indirectly to a better understanding of the ills of the social organism.

It should be stated that in the editing of the lectures for publication they have been expanded and several chapters

added. Illustrations on the screen, presented during the delivery, have been omitted owing to the difficulty of presenting satisfactorily on paper objects standing near the limit of microscopic vision. Moreover, the lectures try to present the chief factors, the human and animal host and the parasites, in action, rather than in the repose simulated by illustrations.

I

PREDATION AND PARASITISM

AMONG the substantial achievements of the biological and medical sciences during the past half-century there stand out three in clear relief: first, the uncovering of the living agents of the most destructive diseases of man, animals, and plants; second, the unfolding of the complex functions of the ductless glands, known as the endocrine system, and the disturbances associated with their over- and underactivity; and third, the discovery of certain food substances, called vitamins, the lack or overabundance of which leads to characteristic diseased conditions. Though there are certain links between the first and the two other fields, the relation is not sufficiently clear or conspicuous at present to justify recognition here. It may be disposed of by the general statement that living parasites or disease germs tend to enter whenever the gates are ajar and any defect or depression in functional activities of the host may favor them.

The relation between parasitism and disease is best formulated by the attitude of scientific research towards them. In his studies of animal life the zoologist frequently encounters animals, especially of the lower orders, the tissues of which are peopled with various kinds of parasites. The host animal to all appearances is normal in its behavior. The physician and pathologist, on the other hand, frequently encounter disease and death in individuals in whom the presence of microscopic parasites hardly suffices to account for the disastrous results. The relatively harmless relationship impresses the zoologist and he studies parasitism. On the other hand the

pathologist is struck with the injury inflicted and his theme is disease and how to protect against disease.

The struggle for existence among living things, both plants and animals, which may be translated into a struggle for food and a search for the easiest way of obtaining such food, has developed two universal habits, the predatory and the parasitic. Plants gain their subsistence from the soil and animals are dependent upon plants and other animals. Certain plant forms subsist upon other plants. The universality of the predatory habit of animal life may best be expressed by the statement that few animals consume prey which they have not killed themselves. Even our birds are valued in proportion to their insect-eating propensities. Herbivorous animals in a state of nature browse on living plants as long as they last. The predatory has probably led by gradual evolutionary steps to the parasitic habit which Leuckart defines as the finding of lodgment and food by one organism on or in another. The frequency with which the student of living things encounters parasitism leads to a certain blunting of our sense of its fundamental significance as a major phenomenon of life. Parasitism may be regarded, not as a pathological manifestation, but as a normal condition having its roots in the interdependence of all living organisms. Giart called attention to a peculiar parasitism of the embryo among mammals. The ovum instead of passing out of the maternal organism, as is true for birds and most lower forms, settles down in the uterus as a real parasite. Even after birth the young are dependent for a time on the mother for their food supply. Parasitism is in a restricted sense the reverse of the predatory habit. The predatory animal is as a rule larger and more powerful than its victim, whereas the parasite is the smaller and weaker. There exists a concealed relation between the two types of life in that predatory habits may have led in some instances directly to parasitism. Certain lower forms

consumed as prey may have quite accidentally found themselves endowed with the capacity to live within the consumer as parasites.

Parasitism has probably worked great changes in geologic ages. Osborn includes it among the important agencies in the extinction of certain species of mammals. Man has aided parasitism in several ways. Unwittingly he has tended to bring together parasites from every region of the earth and to make universal what were originally local diseases. Domestication has entered to protect the animal which in a state of nature would speedily fall a prey to its enemies. But by overcrowding animals domestication favors infection in exposing them to large numbers of parasites from which they cannot escape. Mass production of the same species of plants and animals has favored latent and evolving parasitism. While it may be going too far to accuse domestication in general of breeding disease, it is literally true of a kind of animal husbandry which is unredeemed by that sanitation and care which must be applied to take the place of those self-purifying habits developed by animals in a state of nature. What is true of domestication among animals is within certain limitations also true of the same process among men.

The distinction between the predatory and the parasitic habit is easily made when extremes are considered. There are, however, numerous transitional types which involve an element of both. There are groups of parasites which invade living organisms, destroy them, and then utilize the dead tissues for themselves and their progeny. Some animals, like the mosquito, are in a sense both parasitic and predatory. Even among the bacteria a line may be drawn between predatory and parasitic phenomena. Thus, the bacteria which rapidly invade the animal body and produce fatal septicemic affections are more predatory than parasitic. Parasitism is in a sense a compromise or truce between two living things,

accompanied by predatory processes whenever opportunity is offered one or the other party. The universality of parasitism as an offshoot of the predatory habit negatives the position taken by man that it is a pathological phenomenon or a deviation from the normal processes of nature. The pathological manifestations are only incidents in a developing parasitism. As human beings intent on maintaining man's domination over nature we may regard parasitism as pathological insofar as it becomes a drain upon human resources. In our efforts to protect ourselves we may make every kind of sacrifice to limit, reduce, and even eliminate parasitism as a factor in human life. Science attempts to define the terms on which this policy of elimination may or may not succeed. We must first of all thoroughly understand the problem, put ourselves in possession of all the facts in order to estimate the cost. Too often it has been assumed that parasitism was abnormal and that it needed only a slight force to reestablish what was believed to be a normal equilibrium without parasitism. On the contrary, biology teaches us that parasitism is a normal phenomenon and if we accept this view we shall be more ready to pay the price of freedom as a permanent and ever recurring levy of nature for immunity from a condition to which all life is subject. The greatest victory of man over nature in the physical realm would undoubtedly be his own delivery from the heavy encumbrance of parasitism with which all life is burdened.

Our information concerning parasitism comes from three main sources: (1) the parasitism of plant and animal life in man; (2) the parasitism of plant and animal life in higher animals; and (3) parasitism affecting plant life. Research in parasitism has been enormously stimulated because of the everyday problems involved. The means that have been forthcoming were largely offered with the expectation of so-called practical results. This is true for the diseases of man and for

those of animals and plants. It is plain, however, that the three fields above enumerated have not the same significance. The hosts involved are of widely different standing and dignity and the methods applicable differ materially. The conquest of parasitism among animals and plants has a purely economic bearing. The diseases of these groups are studied in proportion to their value to mankind. The diseases of man, however, have a different significance. Human life, at least in certain instances, is valued so highly that no effort is spared to prolong it even a few days or hours. Methods and processes designed merely to prolong life or to maintain life in a weakened individual are economically wasteful when applied to animal and plant life. We must, therefore, expect to find that certain discoveries and inventions in preventing and curing disease in man are of little or no direct value for animal life, and that the reverse is in many cases equally true. Certain procedures properly applicable to prevent animal diseases may be quite out of the question for man. The methods of approaching the study of parasitism in the three classes mentioned are also quite different in certain respects. The inviolability of human life closes the door to many problems and compels the investigator to make a circuitous route and to rely upon partial evidence and upon the likeness between human and animal diseases. On the other hand, animal life may be sacrificed at any stage to clear up difficulties provided the means are at hand. This is even easier in the study of plant diseases where numerous individuals may be reared and sacrificed without great cost.

With the prevailing conditions as portrayed, we must expect human parasitism to be worked out in the most thorough and detailed manner with no means spared that promise a step in advance. The study of animal diseases would probably not go beyond a certain point were it not that such study frequently supplements the investigation of human diseases

and fills the unavoidable gaps in human pathology. How far the study of the parasitic diseases of plant life may go beyond the economic applicability of results to the preservation of valuable vegetation, to promote our knowledge of animal and human diseases, has only recently been seriously discussed. It is tempting to predict the ultimate merging of the two streams of biological research in the parasitism of the cell in both plants and animals as the final locus of conflict in which the processes may be more or less identical. We must bear in mind the generally accepted statement that no one can tell just how far a newly discovered fact or relationship may prove to be valuable or remain sterile. It is this possibility which justifies research.

Surveying the field of disease scientists naturally asked what were the causes and necessary conditions. Some parasites are visible to the naked eye. These represent a minority. The pathological changes and disturbed physiological processes of parasitism are very largely due to organisms below the range of ordinary vision. Hence the mistakes of the past in an endeavor to interpret the origins and causes of many diseases. Supernatural agencies were invoked and the applications of this interpretation color the pages of history. Later miasmata emanating from the soil occupied the thoughts and formed the basis of speculation. About half a century ago the study of disease as a result of parasitism made a sudden leap forward, largely due to the genius of Pasteur and the rigid experimental technique and insight of Robert Koch. Microscopic organisms had been seen before in tissues but the technique for linking them definitely with disease had been lacking. The peculiar zigzag, often spiral course which research follows towards ultimate discovery was not lacking in the early adventures of bacteriologists but our program does not permit any tempting deviation in the historical direction.

At present we have confronting us a variety of actual and potential living agents of parasitism:

1. The higher animal parasites of which the worms form the largest group. Of these the hookworm and the tapeworm are well known illustrations.

2. Certain moulds similar to those found on spoilt food which cause various skin and lung affections.

3. Certain minute animal forms, some barely visible with high powers of the microscope, consisting of single life units or cells and known as protozoa. The malarial parasite is an example.

4. The bacteria just visible with the highest powers of the microscope and justifiably regarded as forms of vegetable origin, which produce some of the most formidable diseases and plagues of man and animals.

5. A group of organisms smaller than bacteria but still visible under the microscope and cultured with great difficulty, which produce such diseases as typhus and Rocky Mountain spotted fever. They are known as Rickettsia.

6. A large group of organisms too small to be seen with any known device, which pass through the pores of filters restraining the bacteria. They vie with the bacteria in their capacity for destroying human, animal, and plant life. That life with its functions of growth and reproduction can exist in such minute forms is so challenging a concept that some scientists have seriously regarded these viruses as of enzyme or ferment status. Such enzymes, surviving drying, and inhaled, might, according to them, start certain processes in the body cells which in turn would reproduce the invading enzyme for further dissemination.

Up to the present century, the information available concerning the relation of bacteria to disease kept this group out of the category of parasites. They were regarded rather as predatory, attacking organisms. Even as late as 1900, Paltauf

says that the term "disease agent" is much more appropriate than parasite. The objections of earlier bacteriologists to classifying the infectious microorganisms with parasites were due to the absence of any information concerning the existence of complex relations between them and their respective hosts. Bacteria were supposed to be fermentative and putrefactive organisms which penetrated and took possession of dead organic matter in the host. We now know that the microorganisms which multiply in the body are controlled by definite laws governing parasitism and that their invasion of the living body is wholly different from the attack on a mass of flesh. As a rule, putrefactive bacteria are not parasites and evidently cannot become such until many of the putrefactive functions have been repressed and others brought forward and developed. A substantial claim of bacteria to be called parasites is due to the fact that they may survive the disease which they produce for a considerable time in the body. Even before the beginning of the present century it had been recognized that certain infectious diseases are started by recovered or healthy individuals from which the stock of infection is continually replenished. Since then most bacterial diseases are known to owe their continued prevalence either to healthy or to slightly ill carriers.

A survey of the fields open to students of parasitism shows, as might have been anticipated, that those have received the most attention which include the diseases of man and the higher animals. There is, however, an immense storehouse of parasitic forms among the lower types. Taking the ordinary frog which falls into the hands of the physiologist we find on cursory examination the lungs filled with flukes; the intestines containing nematodes, flagellates, ciliates and amebae; the body cavity, filaria; the red corpuscles, hemosporidia; and the muscles, sarcosporidia. Probably others would be found after systematic search. Similar tales might be told of lizards,

snakes, and of exclusively aquatic animals. This form of parasitism is usually of a highly specialized, relatively harmless and stable type. The host animals, however, are not necessarily resistant to all parasites, for the latter may appear as disease producers, often of a highly fatal type, whenever aquatic and terrestrial host species are exposed to them in fish hatcheries and game preserves in unnatural crowding and where, for the time being, these hosts are secure from the natural, predatory enemies. To utilize animals in investigations bearing on parasitism necessitates the difficult undertaking of freeing them from miscellaneous parasites before they can enter any experiment. This difficulty is being met today in the use of the larger domestic and the smaller laboratory animals. It demands the prompt removal of the young from the mother at birth and such further devices in the feeding as will sustain life for a time and at the same time protect the animal from exposure to the parasites of the parents and those carried by insects and in foods.

Coming to the higher animals we find each species the host of a number of parasites which are rarely found in other species. Each has its own fauna and flora, its larger metazoan parasites, its moulds, its protozoa, bacteria, and ultravisible viruses. This is true also of the human race. Among primitive peoples there is little difference in this respect between them and the higher animals. In fact the reports of those who have ministered to the medical needs of tropical natives indicate perhaps a worse condition than that of animals, partly due to association with the white race, partly to gradual domestication which involves a denser population, a more crowded mode of life, and a greater geographical range of activities. The civilized races, thanks to the development of the medical sciences and greater natural resources, have thrown off many diseases, especially those transmitted in foods. The art of cooking and the protection of communities through sanitary

water supplies and sewage disposal systems were the chief agents in controlling intestinal diseases. The microorganisms carried in the air and inhaled are still of great potential danger as well as the source of many minor local ailments of the respiratory tract.

Parasites of plants are of both vegetable and animal origin. Many of the animal parasites are insects. Some are predatory rather than parasitic. Of the remainder there are many highly specialized relationships leading to the formation of galls. Here the host, under the influence of a refined stimulus, builds shelters for the insect brood. The many diseases of plants associated with fungi and bacteria represent all degrees of parasitism from the more predatory type involving the rapid invasion of the vascular system by bacteria to the more highly specialized types as represented by the less destructive and more prolonged chronic invasion by certain groups of fungi. In recent years the existence of many plant diseases due to ultramicroscopic organisms has been demonstrated. The biological and chemical mysteries enveloping these invisible agencies may perhaps be cleared up by plant pathology.

Coming to the seat of parasitism in the body we find scarcely an organ, or a tissue, or even a type of cell which has not been made the home of parasites in some host. Among the larger parasites there are those that are found, for example, in the wall of the esophagus and in the stomach; roundworms or nematodes are constantly found in the peptic stomach of cattle, sheep, swine, and horses. In the stomach of the horse the larvae of certain flies known as bot flies are almost universally present. In the small intestine we find various roundworms and tapeworms. The same is true of the bile ducts. Some occupy the duodenum; others are found in the lower portions of the small intestine. Each section of the large intestine has its own type of entozoa. In the respiratory tract we

encounter the larvae of flies and arachnids. Roundworms occur in the trachea of birds; worms in the lungs of cattle, sheep, and swine; flukes in the lungs of man in eastern countries. The skin is inhabited by various epizoa some of which, like lice, carry fatal diseases. Larvae of flies inhabit the subcutaneous tissue of some of our domestic animals. Among the protozoa, parasites are found in the epithelial cells of the stomach, and of the small and the large intestine. The red blood corpuscles as well as the white blood corpuscles are the habitat of certain protozoa.

Certain bacteria are found in superficial cells of the skin about to be cast off and in the openings of the glandular structures. Definite species are found in the upper respiratory tract, some even attached to the cilia of the epithelial cells. The entire digestive tract is parasitized by various kinds of bacteria, each species being more or less limited to certain sections. Some are found in the mucus of the tubules and others chiefly in the food masses and excreta. Among the fungi we find parasites in the epidermis, in the hair follicles, in the lungs in birds and mammals, and to a certain extent in the digestive tract. The ultramicroscopic forms, whose actual presence may not be demonstrable by microscope or culture tube but whose destructive effects indicate their presence, attack chiefly the skin and the mucous membranes. The sojourn of these various types of parasites in and on the body varies considerably. Some are present and multiply for a short time and die; others may remain a lifetime. As a rule the higher parasites remain longest in the host. The protozoa come next. The bacteria and ultramicroscopic organisms are probably eliminated much faster than the higher and lower animal parasites. This difference is due to their organization, metabolism, and their methods of multiplication.

In applying the measuring stick of disturbed function or disease to this highly diverse cohabitation of two living enti-

ties we find a great range of damage inflicted on the host. The same must be true of the parasite but not so readily detected. Those types of parasitism which are indifferent to the host and according to which the parasites live without abstracting essential nutriment are usually called messmates or commensals. In rare instances parasites have been regarded as actually favoring the host in some way. Such relation has been called mutualism and also symbiosis. The botanist Debary defined symbiosis as a living together, according to certain natural laws, of unlike organisms, that is, organisms which belong to different species or even to different divisions of the animal and vegetable kingdom. That type of parasitism which is injurious to the host has also been called antibiosis.

A most interesting group of parasites comprises those known as intracellular symbionts. These parasites, which include certain fungi, yeasts, and bacteria, have been found chiefly in insects. Each parasite is present in every individual of the species and passes from one generation through the egg to the succeeding generation. They form definite groups and agglomerations of cells, the so-called mycetoma, which have been mistaken for organs. Cells harboring these parasites may be completely filled and still act normally and go through the normal division or mitosis. Some insects contain two and even three different organisms; frequently pigment is associated with such a symbiotic colony. These parasites are so highly adapted that they may be considered as part of the host species. It is conceivable that other highly adapted, very minute parasites exist but that, owing to their constant presence or invisibility, they cannot be differentiated from the other contents of the cell body. Only artificial cultivation may assist in recognizing them but this process is usually applicable in inverse ratio to the degree of parasitism attained.

The existence of very highly adapted parasites doing little recognizable injury naturally suggests the query whether in

the more or less complete absorption of one organism by another the latter does not gain something by the association. Has the host been in position so to steer the evolution of the parasite that some symbiotic or mutualistic characters became highly developed and of use to the host? In general all parasites are regarded as potentially injurious. They are assumed to give nothing in return. It is, however, conceivable that in a long established relation natural selection has brought forward and amplified certain processes of parasites which are useful to the host and which may even become essential to the life of the host species. Among higher forms such a mutually indispensable arrangement exists between plants and the insects which carry pollen from plant to plant, and by this means serve as exclusive agents of fertilization for many species. Certain groups of plants sacrifice some of their pollen which the insects use as food for themselves or their brood. Enough is left, however, to carry on fertilization successfully. Others produce nectar, a substance provided only for the insect visitor and of no direct use to the plant itself. Other plants provide special cell structures and tissues to be used as food by the insect. A similar give and take seems to have been determined for the leguminosae and their root nodules. The microorganisms contained in the nodules are bacteria more or less modified by association with the tissues of the plant host into so-called bacteroids. The sum total of researches points to a parasitism of the microorganisms which may even be injurious to the host. But the fixation of nitrogen carried on by the bacteroids largely overbalances injurious effects since the nitrogen compounds are utilized by the host plant.

A well known illustration of symbiosis is the association of certain algae with fungi. The two together are known as lichens which grow as colored incrustations on trees and stones. Debary and others have shown that the physiological

processes of the algae and fungi forming the composite plant mutually supplement each other. O. Hertwig and others later on called attention to the association of unicellular algae with radiolaria and actinia as mutualism or symbiosis. The continued exploration of lower forms of life will undoubtedly reveal many other forms of symbiosis as well as highly specialized forms of parasitism. In studying the wood-eating habit of termites, Cleveland has pointed out that the many protozoa in the digestive tract of these ants contain particles of wood which had been eaten by their hosts. Through certain ingenious methods of ridding the termites of their intestinal fauna without injuring the ants themselves, Cleveland showed that the latter were unable to survive without their parasites. A pressure of 5 to 6 atmospheres of oxygen was capable of "defaunating" the termites. Evidently certain species of this group are unable to digest their food and a definite symbiotic relation with unicellular forms of life enables them to exist.

The problem of mutualism has been debated with special reference to the flora of the intestinal tract of higher animals by Metschnikoff. That this problem should command attention is obvious when we consider the large numbers of bacteria and protozoa in the digestive tract. In man and the higher animals the residuary contents of the lower portions of the digestive tract are particularly subject to the action of bacteria. This is true of the entire large intestine in mammals and the ceca of birds. About two-fifths of the dry weight of fecal matter is represented by bacteria. In cattle the three stomachs which prepare the food mechanically for the peptic digestion going on in the fourth stomach are the homes of bacteria and various species of protozoa. In the horse the enormous capacity of the colon suggests some helpful activity of bacteria. Two ways of attacking this problem have been under trial. One is to substitute one kind of flora for another

experimentally and watch the effect. This method was championed originally by Metschnikoff. The other is to raise animals free from bacteria and to study their metabolism. The first method is not adapted to inform us whether bacteria are or are not essential to the digestive processes. It bears rather upon questions of the injurious character of certain species and the beneficent action of others. With reference to the other method of attack, Pasteur over fifty years ago asked the question whether it is possible to rear animals without intestinal bacteria. The answer to this question was first attempted by Nuttall and Thierfelder in 1895. Fetal guinea pigs were removed from the uterus by an abdominal operation and placed in an apparatus where they were supplied with sterile air and sterile food. One guinea pig was kept alive for nearly ten days. This experiment proved that intestinal flora were not essential to life, but it did not determine whether they were favorable to it. In 1901, Mme. Metschnikoff made a not very successful experiment with tadpoles, probably on account of the technical difficulties encountered. The control tadpoles grew much faster than the sterile ones probably because of the unsatisfactory food of the latter. She concludes that bacteria are essential for the continued existence of tadpoles. Schottelius next took up the problem with sterile chicks. His conclusions were that intestinal bacteria are necessary for the continued life of fowls for his experiments showed that sterile chicks died within three weeks or much earlier while controls were thriving. Sterile chicks subsequently fed with cultures of bacteria rapidly reached a normal condition. According to Schottelius intestinal bacteria are necessary to prepare the ingesta, to assist in absorption, to stimulate peristalsis, and to keep down pathogenic bacteria accidentally ingested. Bogdanow experimented with ova of sterile flesh flies on sterile meat. Only after a sterile solution of trypsin had been added could the flies be made to develop. The infer-

ence was that the food of flies requires preparation by bacteria. E. Wollman in 1911 was able to raise sterile flies. Although those used as controls developed faster, the others caught up with them after a time. Cohendy, continuing the work of Schottelius on chicks, with a different technique, came to the conclusion that sterile chicks are as vigorous as controls and more resistant to hunger, thirst, and exposure to moisture. The most successful experiments were made on kids by Küster who had assisted Schottelius in his work. The fetuses were removed by Cesarian section and placed in an apparatus supplying sterile air and food. Kids were kept from thirty-five to forty-three days free from bacteria and did as well as controls. Küster's experiments demonstrate definitely that the intestinal flora is not essential to goats, possibly not to other mammals. Cohendy's results indicate the same for chickens. Whether bacteria are favoring or not, whether injury or benefit predominates may require much more experimentation. Jacques Loeb and Northrop raised a number of sterile individuals of the banana fly, *Drosophila,* on sterilized baker's yeast. No other of the many culture media tried was suitable for the complete development and continued rearing of these flies. They thus proved that the existence of this fly depends primarily on yeast and incidentally call attention to the possible function of microorganisms in the intestines of higher animals.

The evidence that parasitism, as it affects man and the to him economically important animals and plants, has any concealed symbiotic value is still to be furnished. Science is rather in favor of the estimate that parasitism if not harmless is injurious. In the case of the parasitism of the digestive tract sporadic injury is indicated by the invasion of the blood and tissues at times by *B. coli, B. lactis aerogenes, B. tetani, B. chauvoei, B. welchii,* and other obligatory and facultative anaerobes which parasitize the intestinal tract. Certain tempo-

rarily favoring conditions may convert such messmates into aggressive tissue invaders. For many years the problem of auto-intoxication or self-poisoning by bacteria living in the lower intestinal tract has occupied the attention of physicians. That so-called toxins or poisons set free by bacteria may be absorbed into the system seems a reasonable inference. The problem is complex since it involves a number of factors. It, however, emphasizes the importance of maintaining an absolutely normal functioning of the whole digestive system.

Granting the existence of parasites which are so intimately adapted to the host that no disturbance is manifested and that they may even be indistinguishable from the host tissues, we are under no illusion that many are injurious and destructive to their environment in the host. The relation between parasite and host is essentially a conflict for subsistence and in the last analysis a problem of cell metabolism.

Virchow over fifty years ago formulated our subject as follows: "That relation, the solution of which is the real nucleus (or kernel) of pathological, or, expressed in a broader way, of medical research concerning these forms of disease I have formulated as the struggle of the cells with parasitic microorganisms or, more briefly though not less correctly, with bacteria. Evidently two living microorganisms here oppose each other as enemies. The microscopic cells, the vital elements of the body on the one hand, the still smaller bacteria and fungi, these smallest plants, on the other. Both are endowed with a life of their own, therefore with an activity and with forces of their own. Which is the assailant? How does he make his attack? What qualities enable the other to resist? Which of the two is destroyed? These are the questions that need an answer. That disease is a struggle is an old thesis. By a natural philosopher of Hegel's school it was formulated as a struggle of life with death and might have sufficed for him. But life, as such, cannot fight, but only the

living being, and death is no definite opponent but merely a negation."

Virchow was cognizant of the fact that parasitic and invasive organisms have a way of protecting themselves. This aspect of the problem was for a time lost sight of. Although the host-parasite relation was regarded as a struggle between two living organisms, the sympathy and the cheering and the mental betting of the investigator were always on the side of the larger host. Every bit of evidence indicating some resistance on his part was brought to the surface, analyzed, and utilized whenever possible with the aid of vaccines, serums, and the like. However, in recent years the conception that parasites having maintained themselves over indefinite periods of time must have some adaptive mechanism for protective purposes has gained ground and we are gradually approaching the view that the relation between host and the invasive parasite is a highly complicated give-and-take process which must be looked at from a biological standpoint and the various factors studied impartially before medical applications can be regarded as resting on safe foundations. It is difficult, however, to tear oneself away from the older standpoints. In the chapters that follow, the factors of parasite resistance will be emphasized wherever they may appear. They are, however, highly elusive owing to many difficulties, the most obvious being the minute size of the parasites which stands in the way of any satisfactory structural or morphological analysis.

In search for some underlying explanation which would harmonize the many diverse relations between host and parasite, I have at various times and occasions presented the hypothesis of two factors, one of offense and one of defense, characterizing the behavior of both host and parasite. The attempt to survive and multiply or reproduce in another living organism is assumed to involve two quite different procedures, one for active injury, the other for more passive

self-protection. It is this theory which serves as a guide in the pages that follow. It would be naïve to regard the living world as adhering too rigidly to one expression of this concept of parasitism. Each host-parasite relation has developed its own application of the law so that no two may be regarded as identical. The offensive or the defensive function may dominate. One may be entirely submerged in the other. The formulation of a principle in a restricted biological field usually leads to an overestimation of its rigidity or stability and to its direct application to all the known relatives of the species in which it first came to light. Sooner or later, however, if not superseded, it tends to find its level and take its proper place, usually a modest one, among biological principles or laws. No attempt is made to place any teleological significance on the two factors. All that can be postulated is the universal struggle of living things to survive, and in this struggle the fundamental biological reactions gradually range themselves by natural selection under these two categories of offense and defense.

Parasites have usually been regarded as degraded forms of free-living species. This view is not wholly true. Degraded they may be in form but hardly in function. For as we shall see, the forces necessary for parasites to maintain themselves and multiply in the hostile environment of living animal tissues are not to be regarded as below those needed in the free-living state. In each the requirements are adjusted to the immediate environment. The free-living species must have more varied, more diversified protective activities, whereas parasites must concentrate theirs against a few dominant anti-alien reactions of the host.

II

THE LIFE CYCLE OF PARASITES

FOR convenience in grouping our data we may divide the life of parasites into four critical stages or periods: (1) their entrance into or invasion of the host; (2) their multiplication within the body of the host; (3) their discharge, emigration or excretion outwards; and (4) their active or passive transfer or transmission to another host.

The entrance of parasites into the body tissues is effected through several different portals. The skin is the one most frequently used. The immediate entry may be through accidental wounds causing breaks in the normal continuous protecting covering. Entry may also be made by piercing the skin, as does the hookworm. Or the parasites may lodge in the hair follicles and ducts of sebaceous glands. Thence by a process of inflammation deeper parts may become involved. The mucous membranes in direct or indirect communication with the exterior represent the other large exposed surfaces through which many parasites enter the body tissues. A distinction should be made between entering the various natural openings of the body and entering the tissues proper. This distinction I shall maintain by referring to the one as body invasion and the other as tissue invasion. Thus swallowing typhoid bacilli does not necessarily imply invasion of tissues. After entering the mouth, their course is not definitely known but it is fairly certain that individuals may ingest these bacilli without suffering actual invasion of tissues.

In general, bacteria and related microorganisms cause a so-called reaction at the place of tissue invasion. The malig-

nant pustule of anthrax, the ordinary boil, and the hard chancre of syphilis, are instances of such reaction. In certain other diseases, swelling of the nearest or regional lymph nodes or "glands" is indirect evidence of a nearby invasion. In tuberculosis and in bubonic plague it is a fairly reliable guide. There are, however, exceptions to the rule that local disturbance may follow tissue invasion. If it does in such exceptional cases it is overlooked. When the invasion of the body is by way of the mucous membranes, no warning is given and search for the immediate locus of invasion is usually out of the question until it is too late to distinguish between primary and secondary injury. To produce disease invasion of the body tissues is not always necessary. The habitats of Asiatic cholera and dysentery bacteria are the folds and recesses of the intestinal mucosa where their multiplication is associated with local destructive effects and the absorption of poisons or toxins by the host tissues.

The tenacity with which certain types like paratyphoid and typhoid bacilli maintain their motility suggests the possibility that motility is a useful or perhaps even necessary qualification for their pathogenic activities. Nothing is definitely known, however, of their active penetration of mucous membranes independently of lesions and we are left to conjectures. Once in the tissue spaces and vessels motility may be a hindrance, for agglutination of the flagella goes on so much more readily than body agglutination.

The mode of invasion through minute wounds is of more theoretical than practical importance in many infections, for minute wounds must be more or less common in the integument and mucous membrances of both man and animals, and all that is necessary is a relatively heavy infection so that the wound and the invader may be brought together. The procedure of shaving even when carried out with great care opens the skin of animals to infectious agents gently placed upon it.

Even gently rubbing in of certain virulent cultures when not preceded by shaving may cause fatal diseases among laboratory animals, such as guinea pigs and rabbits. In general it may be said that our information in regard to the mode and often the locus of invasion is based on general, indirect evidence because of the small numbers and the minuteness of the invading objects and the difficulty of distinguishing or recognizing individual invaders.

Turning to the protozoa we find the evidence clearer owing to the characteristic morphology of most of these forms. There is, however, a lack of local pathological indications which, as stated above, are so useful in tracing portals of entry of bacteria. On the other hand this difficulty is in part compensated by the more restricted, specialized paths of this class of parasites in the body of the host. There are usually well developed locomotory phases in the flagellates, the sporozoa, and the ciliates. The forms assumed by the motile stage are such as may most effectually penetrate between and into epithelia. This is particularly true of the coccidia in which the products of both sexual and asexual multiplication are falciform in outline and mobile. Even amebae have the power of moving, in some species, with considerable rapidity but it is still doubtful if the pathogenic types enter the depths of the mucous membrane unaided by previous lesions, however slight. With certain protozoan and higher parasites, a close parasitic relationship with stinging and biting insects enables them to enter and leave the system without any active participation on their part. The various parasites of the red blood corpuscles of mammals and birds are thus favored. They are, however, compelled to invade actively or attach themselves to red blood corpuscles or leucocytes after their passive entry into the blood of the host.

Among the higher entozoa or worms active invasion may be present and in at least one group, the sclerostomes or hook-

worms, complicated life cycles result following the penetration of the skin, possibly the mucosa as well. Their migration by way of the lungs and the final attachment of the adults to the mucous membrane of the small and large intestines have been traced. Here also the distinction between body and tissue invasion is of value in that the former, with many forms, is passive in the ovum and active in the tissues afterwards. Thus the larvae of *Trichinella spiralis* are passive when ingested in the flesh of swine but active later when invading the muscular tissues of the host.

There is one interesting phase of the life cycle of certain of the higher parasites which fits in between the invasion and the final location of the sexually adult parasite. Certain nematodes after entering the body undergo one or more metamorphoses associated with moulting, the most important phenomenon being a change in the mouth parts. These transitional stages from larva to adult usually go on in localities different from those inhabited by the adult worm. Thus the larva of the large hookworm of the horse lives in the anterior mesenteric artery near its origin. Here, embedded in a coagulum or thrombus, one or many larvae live for a given, unknown period. Examination of the contents of such so-called aneurysms leads to the discovery of stages during which the last moult is enclosing a worm with adult mouth parts. The moult itself shows a mouth structure quite unadapted to the final function of the worm, that of firm attachment to the mucous membrane of cecum and upper colon. After the final stage is reached, the worm migrates to the mucosa, or else is carried passively to the terminal branches of the mesenteric artery and there works its way to the lumen of the intestine. This preliminary stage within certain tissues is quite common among the hookworms of domestic animals. Encystment within the mucous membrane or submucosa is most frequently encountered, resulting in the so-called worm-nodules

which have been at times diagnosed by overzealous and undertrained health officers and meat inspectors as products of the tubercle bacillus. This intermediate development evidently cannot take place at the site occupied by the adult because of larval mouth parts and perhaps other deficiencies. A quiet berth within the depths of the mucosa or within blood vessels meets the difficulty. The tissues involved react with the end product, a degenerated caseous mass of host cells in which the worm remains embedded until ready to pierce its way to the surface. So far as is known no encysted stage of the human hookworm has been found. According to Loos, two moults within the human host precede the adult stage. The mouth parts of this species during the larval stage may be like those of the adult and not require encystment. It is interesting to note here that the early stages of certain intestinal parasites, including the tapeworms and some roundworms, are spent within intermediate hosts. When the parasite reaches the definitive host it is prepared to take its place with the adults.

Leaving now this first stage of the cycle for the time being, let us follow parasites in their movements after entry into the host. Here their chief function is to multiply and produce a progeny large enough to reach another host eventually. But before this process begins they must localize somewhere in the host. We may consider the animal body a huge commonwealth in which the entering parasite is restricted to a given territory or a given stratum of society. It is forced into a given habitat—in the same way as free-living organisms are restricted to definite habitats in nature. The original habitat or home of any plant or animal is usually understood to be the place where it is found either exclusively or whence it has spread to other localities. Certain plants cannot be raised in localities other than where they are naturally encountered, excepting under great difficulties. Other plants whose origi-

nal habitat was restricted to a certain country or territory have been easily cultivated elsewhere. Most useful plants have been disseminated from some one focus. The discovery of the tobacco plant, the peach tree, the tomato, the Indian corn, and the potato plant, and their gradual introduction into nearly all countries are familiar to most readers. Certain animals are also restricted to definite territories or zones. Through artificial means such animals may be kept alive beyond their natural habitat in zoological gardens. The conditions which unite to favor certain animals and plants in given regions and which prevent their obtaining a permanent foothold in others are numerous and their interaction forms complex resultants which are as yet poorly understood. Parasites are also to be found in certain tissues or organs of the body; some occur exclusively in certain well defined situations, others are less narrowly limited.

PREDOMINANT, EXCLUSIVE OR FINAL LOCATION OF PARASITES

SKIN AND SUBCUTIS

Metazoa	*Protozoa*	*Bacteria and Fungi*	*Filtrable Viruses and Undetermined*
Lice	Oriental sore	Staphylococci	Foot-and-mouth disease
Fleas		Streptococci	Measles
Bed-bugs		Tubercle bacilli	Smallpox
Mosquitoes		Frambesia	Molluscum contagiosum
Larvae of certain flies		Glanders	
Demodex follicularum		Leprosy	
Filaria medinensis		Syphilis	
Sarcopsylla penetrans		Trachoma	
Sarcoptes scabiei		Actinomycosis	
		Favus	
		Madura foot	
		Sporotrichosis	
		Tinea versicolor	
		Trichophyton	
		Blastomycosis	
		Pathogenic yeasts	

Mammary Gland
- Paratyphoid bacilli
- Staphylococci
- Streptococci
- Tubercle bacilli
- Malta fever
- Actinomycosis

Digestive Tract and Appendages, Salivary Glands, and Bile Ducts

Higher Parasites	*Protozoa*	*Bacteria*	*Ultramicroscopic Organisms*
Many roundworms, tapeworms and flukes	Coccidia Ameba Ciliates Flagellates	Cholera bacilli Dysentery bacilli Paratyphoid bacilli Typhoid bacilli	Rabies Rinderpest Swine pest

Genital Tract
- Normal
  - Trichomonas vaginalis
  - Smegma bacilli
- Pathological
  - Trypanosomes (horses)
  - Gonorrhea
  - Syphilis
  - Tuberculosis

Upper and Lower Respiratory Tract
- Lungworms (cattle, sheep, swine)
- Paragonimus westermanni
- Pentastomum
- Meningococci
- Pneumococci
- Streptococci and Staphylococci
- Tubercle bacilli
- Foot-and-mouth disease
- Glanders
- Influenza
- Poliomyelitis
- Septicemia hemorrhagica

ADAPTATIONS TO TISSUES AND ORGANS NOT IN IMMEDIATE RELATION TO EXTERIOR

Muscular tissue	Cestodes (larval stage)
	Trichinella
	Sarcosporidia
Blood vessels	Schistosomum hematobium
	Filaria larvae
	Trypanosomes
	Malaria
	Piroplasms
	Hemameba

The great variety of habitats of parasites has been referred to. It was stated that scarcely any cavity, organ, tissue, or cell escapes being the seat of some parasitic organism. If we tabulate the various exclusive or preferred sites it becomes evident that they are in large part controlled by the conditions which favor exit from the body of the host. The tables show that there are few parasites known which do not live at some stage of their existence in or immediately under the skin or the mucous membranes. That this superficial habitat is an adaptation necessary to the continued life of the parasite species seems the simplest explanation. Those parasites which occupy tissues not in close or immediate association with the exterior are aided by special devices in their escape from one host to another, or else they are individuals which have lost their way.

Special restricted habitats are the rule rather than the exception among higher parasites. *Ascaris* is always found in the upper portion of the small intestine, in or near the duodenum. *Oxyuris* in its adult stage occurs in the cecum. *Trichuris* is attached to the mucosa of the cecum. Tapeworms are found only in the small intestine. Hookworms of one host species may be in the duodenum, in another in the cecum. One species of bot-fly in the horse is attached to the cardiac expansion of the stomach, another to the pyloric end. Certain protozoan parasites have their habitat in definite cells of the

body, some in the intestinal epithelium, others in renal epithelium, still others in red blood cells or in leucocytes. Sarcosporidia and trichinae enter muscle fibers. With bacteria there is no such sharp delimitation of habitat. At first thought one might think that there is absolutely no restriction placed upon bacteria in their localization and multiplication in the host. This view is largely due to the want of thorough study of this phase of the subject. It is true that pathogenic bacteria may be encountered anywhere in the body. But this is also true of *Ascaris,* during fevers when the worms begin to migrate, or after accidents such as gunshot wounds or in perforation of the intestines. The reason for their straying is easily apprehended, but for the microscopic and ultramicroscopic bacteria the distribution cannot so readily be explained.

The significance of the localization of parasites is perhaps best understood by taking together entrance and exit and noting the various ways in which these two stages are linked together. For many parasites which settle down in the various layers of the skin or immediately beneath in the subcutis entrance and exit coincide. The intimate mechanisms of the two processes are, to be sure, not identical and perhaps very different but this need not concern us. All infectious skin diseases belong to this group. The parasites may produce resistant spores of some kind in abundance which require only proximity of one host to another to continue the life cycle of the species, or they may protect themselves through capsules and in other still unknown ways. Certain organisms belonging to the group of animal parasites such as lice and itch mites, which have the power of locomotion, to a certain extent can migrate actively from host to host. Yet even with them, passive transmission by other agencies is of major importance as their movements at best are very slow.

The movement of parasites from one host to another is in part necessitated by the fact that the host may die and with

him the parasite. This is true more particularly of parasites whose seat is below the surface of the skin and whose exit requires some destruction of tissues. The various kinds of skin parasites which vegetate in the upper layers of the skin and the vermin can leave the body even after death, or be carried by objects coming in contact with the skin and clothing of the dead. The parasitism of the outer integument is thus the simplest type. The parasite needs only to provide for abundant offspring and the transfer is readily effected by direct contact or indirect contact through objects of various kinds.

A second type of invasion and excretion by way of the same channels is represented by the various forms of infection of the respiratory organs, notably in influenza and pneumonia. In pulmonary tuberculosis the evidence points to a direct inhalation of tubercle bacilli into the lungs, the multiplication there, and the subsequent discharge outward through the same channels in the sputum. That tubercle bacilli may in certain cases enter the lungs by way of the blood from some other organ is also established, but it is probably the exceptional rather than the ordinary route. The cycle of this microorganism has been much debated. Baumgarten over forty years ago maintained stoutly that the bacillus was transmitted in the ovum or the semen and that infection was therefore germinal and as old as the individual affected. More recently Von Behring contended for an infection through the digestive tract at an early age. The later appearance of phthisis is, according to him, the lighting up of an old parasitism in a new organ, the lungs. In the prosecution of a problem of this kind we must distinguish between the most frequent route and aberrant routes. The practical importance of knowing precisely what is the predominant route of tuberculosis becomes clear when we follow these theories to the obvious conclusions to which they lead. If the infection is germinal the sub-

sequent efflorescence of the lung disease with its discharge of myriads of tubercle bacilli often over long periods of time is of no practical consequence. The individual exposed to the bacilli is either already infected or else immune on account of age. Von Behring's theory minimizes the importance of all infection after infancy because the adult or adolescent is already infected and therefore refractory. Only the very young need to be shielded and these not too scrupulously so that they may not be deprived of the protecting dose. This theory is insofar in line with certain general principles in that most infectious diseases which have prevailed over long periods of time tend towards childhood or infancy as the most favorable soil because of the immunity of later life. As a rule, however, such diseases have little or no influence on later life whereas tuberculosis is most destructive after childhood. It is argued that the lungs are reached last in tuberculosis and are most susceptible, but there is no reason known why the tubercle bacillus should not reach the lungs very early in the course of the infantile disease. This brief discussion shows the importance of a clear understanding of the predominating cycle so that practical considerations of prevention and cure, so costly to society, may have a stable basis and be in no danger of a complete reversal. Concerning the mode of entry of the group of nematodes which live in their adult sexual stage in the lungs of cattle, sheep and swine no conclusive evidence has been presented. These worms inhabit certain regions of the lungs and the sexual products of the worm are coughed up and discharged outward.

The next somewhat more complicated type of invasion and excretion is by way of the digestive tract. The table shows parasites multiplying either in the lumen of the digestive tube or in the mucous membrane. Of these, many pass in by way of the mouth through the stomach and lodge in the small or large intestine where multiplication goes on. The progeny is

discharged in the feces. Among the bacteria which multiply within the digestive tube or its walls are the cholera and dysentery bacteria. Other bacteria, which enter with the food, such as the typhoid bacillus, multiply in the walls of the intestines. Destruction of tissues sets them free. It is a debated question whether they do or do not also multiply on the mucous membrane in the intestinal contents. The virus of rinderpest and hog cholera probably escape in the same way as the typhoid bacillus. Their entry appears to be in the food.

Among the higher parasites the nematodes or roundworms present the simplest cycle. The ovum with ripe embryo within is taken into the mouth with the food. The embryo is set free in certain segments of the tract and becomes sexually mature. Ova are discharged and pass outward in the feces to infect another host either immediately or after a period of development in the soil. A similar cycle or portion of a complete cycle is passed through by trematodes and cestodes, by certain insects whose larval development goes on in the stomach. Among the protozoa, the coccidia and certain ciliates, flagellates and amebae pass through the digestive tube in the same way. This route into the intestines has been made possible by special adaptations of the migrating stage to the destructive fluids of the stomach. Parasites of the true or peptic stomach among animals are far less numerous than those living farther along in the small and the large intestine; there are, however, such in practically all species. The capacity for withstanding the acid gastric juice is thus possessed by certain higher parasites. It is, however, improbable that a species exists which in its actively growing stage can resist both peptic and pancreatic fluids, for no species is known which inhabits both stomach and intestines.

Besides these three relatively direct modes of entry and exit there are a number of others which are built up by a recombination and modification of these. Thus parasites which

leave by way of the skin may have entered by way of the respiratory, digestive, or genital organs. Similarly those which leave by way of the digestive tract may have entered by way of the skin or the respiratory tract. Some parasites pursue long and devious routes before arriving finally at the site where reproduction and outward discharge of the progeny normally occur. The tracing of these routes has led to some of the most unexpected and fascinating discoveries of modern biological science. The cycle of the *Oestridae,* certain flies whose larvae live under the skin of animals, is equally interesting. Cooper Curtice has shown that the larva taken into the mouth passes through the walls of the esophagus into the muscles of the back. It migrates through these until it reaches the subcutaneous tissue of the back. Here it continues its development as oxwarble until it is ready to penetrate through the skin outward and drop to the ground where it pupates and eventually emerges as an adult fly.

The cycle of the hookworm has been made familiar to many living in the infected territories by the preventive work of the Rockefeller Foundation. The progeny leaves the intestines as an ovum within which the embryo rapidly develops in moist earth. It invades the next host by penetrating the skin, usually of the bare foot. The irritation thereby produced is known as ground itch. The larva enters a vein and is carried through the right side of the heart to the lungs where it leaves the circulation and migrates via the air tubes into the esophagus, stomach, and duodenum. Here it attaches itself and becomes sexually mature. A crop of fertilized eggs completes the cycle. The larvae have been followed in this cycle after having been applied to the skin of the monkey. *Klossiella muris,* a coccidium of the mouse, enters the digestive tract in the food and leaves by way of the urinary tract. The parasite settles down in the kidney and continues its development in epithelial cells. The spores pass down the ureter and out-

ward in the urine. Another protozoon, the hepatozoon of Miller, enters the digestive tract of the rat in the body of a louse consumed by the rat, and its progeny leaves by way of the blood drawn by a louse. Metzner, in a series of tests with gastric and duodenal secretions upon the oocysts of coccidia, found that the gastric juice cannot act upon the cysts to liberate the contained sporozoites. Even duodenal secretion is only very feebly active. When, however, the pancreatic secretion has been stimulated the intestinal fluid rapidly liberates the sporozoites, probably by digesting plugs in the micropyle of the cyst. This ineffectiveness of gastric secretion was not restricted to the host (rabbit) but the dog's gastric fluid was equally ineffective. Among the eruptive diseases, the microorganisms probably enter the blood by way of the respiratory tract, having been inhaled in the air. They presumably leave the body in the skin eruptions. Owing to the fact that the microorganisms of these diseases are ultramicroscopic or still unknown, their cycle as given is largely conjecture based on clinical observations.

In the case of *Trichinella* and sarcosporidia the intestinal route departs somewhat from the usual type. Trichinae are ingested as larvae in the flesh of the host. The life-cycle starts with the larval stage and, instead of stopping at the egg stage, goes on to the larval stage in the muscular tissue. The parasite passes the cycle from larva to larva instead of from ovum to ovum in one host. Similarly the protozoan muscle parasite, at least in the mouse, must be ingested in the flesh by the next host. A further step in the modification of the cycle of intestinal parasites is the introduction of a so-called intermediate host. Thus certain species of tapeworms have adopted this mode of transmission. *Taenia solium,* the pork tapeworm, passes from man to swine and back to man, *Taenia saginata* from man to cattle and back to man, *Diphyllobothrium latum,* the fish tapeworm, from man or other mammal to

fishes and back again. Insects serve as intermediate hosts for some tapeworms. The progeny of these parasites leaves the primary host via the intestinal tract to be picked up in the food, contaminated with fecal matter, by the intermediate host. These relations are obviously the outcome of the predatory habit. The primary host eats the intermediate host and thereby acquires the parasite.

The habit of certain insects and arachnids to live as temporary or permanent parasites upon the blood of larger animals has led to the establishment of a complex cycle, between the two, of a third, usually a microscopic parasite. Nearly every one of the many parasitic ectozoa of man has been shown to transfer some parasite to the latter. Thus mosquitoes are known to transmit malaria, yellow fever, and filariasis; biting flies, certain trypanosomes; bedbugs, fleas, and lice, typhus fever and certain other parasites. Among the ectozoa of animals the arachnids known as ticks transmit a variety of protozoan diseases. The disease-producing microscopic parasite is purely passive in this transfer. It has adapted itself to a life in the blood of the mammalian or avian host where it is readily accessible to the secondary or intermediate host when the latter feeds upon the blood. In filariasis, due to a threadlike worm, a further adaptation of the larval filariae has taken place, in that some species appear in the peripheral blood of the host in largest numbers when mosquitoes are most active. So far as is known the established routes of animal parasites are not departed from, or if they are, the strayed parasites are suppressed. The higher or more complicated the organization of the parasite, the more restricted the successful route. Man may intervene and modify the route as when blood containing protozoan types such as those of malaria and the piroplasms is transferred directly with the syringe from one host to another. This artificial

route is possible only when indefinite asexual multiplication in the blood exists as part of the cycle.

Coming to the bacteria, we find entry and exit not so definitely restricted. Thus the tubercle bacillus may enter through wounds of the skin and mucous membranes, in the inspired air by way of the lungs, and in the food through the mucous membranes of the intestines. This bacillus may be discharged in sputum from the lungs, through the intestines in swallowed sputum or when ulcers are present, from the kidneys through the urine, and from the skin in lupus and other forms of skin tuberculosis, and from deeper parts in the cheesy masses from cold abscesses. Nevertheless the route of bacteria through the body is not so haphazard as may appear from investigations, any more than stragglers or deserters indicate the main route of an army. There are still many facts to be more accurately interpreted and their relative values adjusted in the bacteriology of infectious diseases before we may speak definitely of the routes of pathogenic bacteria in their relation to the tissues of the host. If the difficulties inherent in tracing minute objects of nondescript forms are great, they are practically insurmountable at present in the study of the so-called filtrable and ultramicroscopic parasites. The entry can only be conjectured from data gathered by clinical medicine and pathology. The exit indicated by injury or lesions en route may be traced by testing for the specific infection in the secretions and excretions upon susceptible animals if such can be found.

Between the entry of parasites and their exit a most important stage of multiplication or reproduction occurs. The more numerous the progeny discharged by parasites, the greater the chances for reaching another host. Hence those individuals of any species of parasites which are most prolific and whose progeny leaves the host in largest numbers are likely to survive and give character to the species. Among

the higher animal parasites multiplication takes place by means of the process of sexual reproduction. Large numbers of ova are produced by these parasites continuously during the life of the female. Obviously the numbers in the progeny are tuned to the dangers and losses encountered in transit. Among certain species of intestinal worms the discharge of ova may continue for years. In some species the female becomes converted into a relatively huge deformed receptacle full of ova. This is true of the worm which inhabits the peptic glands of the proventriculus of the common fowl. *Oxyuris* likewise becomes greatly distended and dies when discharged, thereby liberating the ova. The female of the species of insect known as jigger swells up under the skin under the pressure of the maturing ova.

Most of the higher parasites, such as the worms, do not produce a second generation in the same host. In other words they do not carry the process of reproduction beyond the egg stage. Thus a single fertilized ascaris egg swallowed gives rise to only one worm in the intestines. The ova of those worms which become mature pass out. To invade the same host again, they must be swallowed. A few of the higher parasites overstep the usual limit. Trichinae do not pass out as ova, but migrate within the same host and settle down finally as larvae in the muscles, where they wait indefinitely for the next host to eat and entertain them. In one species of worm, *Bilharzia,* or *Schistosomum,* which lives in the portal system of the blood vessels in human beings, the ova which finally reach the lumen of rectum, bladder and associated organs from the veins do so at considerable cost to the host. The injury inflicted by the spined ova in their outward movements makes up what is known as Bilharzia disease.

Contrasted with these parasites multiplying only as a result of sexual processes are the bacteria among which multiplication occurs by simple fission. A sexual process is

unknown. An indefinite number of bacteria are produced in this way from a single bacterial cell. The rate of multiplication varies, however, very much according to the environment. In the tissues of the animal the rate is far below the optimum of the culture tube. In the latter it varies from the beginning to the end. At first there is a well marked retardation or lag. This gives way to a rapid increase in numbers until retardation again begins, which terminates in complete cessation of growth. The influences at work in the tissues and in the culture fluid to check growth are manifestly very different from one another. An interpretation of the former comes under the subject immunity to be discussed farther on. Cessation of multiplication in the culture tube is due to accumulation of various secretory products of the bacteria themselves together with the exhaustion of certain nutrient elements and changes in reaction.

Among certain of the protozoa both types of reproduction go on in the host. The asexual reproduction gives rise to a definite or indefinite number of individuals. These in turn go through the same process again or become sexually differentiated and in the process of sexual reproduction which follows a large or small number of offspring is produced. Usually this number is fixed and aids in classification. This progeny of sexual reproduction does not gain a foothold in the same host but must pass on to another. Not all protozoan parasites are known to reproduce sexually, but according to some authorities this absence of sex forms is due to the fact that we have not yet discovered them.

For medical science and the medical art this second phase of the parasitic cycle is of prime importance for the degree of physiological disturbance or disease and the amount of injury produced is directly dependent on the rate and manner of reproduction of the parasites. Of those whose progeny retains no foothold in the same host, the injury varies with the

number of ova or larvae entering the body. The appearance of a fresh generation in the same host, as with *Trichinella spiralis,* even if only a fraction of development takes place, is a signal for disease. In filariasis the progeny inhabits the blood as minute larvae, usually in large numbers, for an indefinite series of months and perhaps years. No further growth takes place. These larvae do not act as pathogenic agents and the lesions of filariasis are to be ascribed to the adults which live in and obstruct limited territories of the lymphatic system. Among the protozoa and bacteria, which multiply more or less indefinitely and which load the host with an unknown series of generations, disease is rarely absent.

The rule cited above that the progeny of parasites continuing in the same host is the only cause of injury has a few exceptions which are of importance clinically. In parasitism due to hookworm and the fish tapeworm severe anemias may appear, the immediate cause of which is not fully understood. In general, however, the injury caused by higher animal parasites is due to large numbers introduced into the body or to what might be called an excessive invasion. Most parasites otherwise harmless may become dangerous when present in large numbers. The injuries inflicted are on the whole mechanical, being due to temporary obstruction of small intestines, plugging of the common bile duct and the pancreatic duct (*Ascaris*); invasion of intrahepatic bile ducts (tapeworms of sheep, *Ascaris*); thrombosis or plugging of arteries (sclerostome of horses); intracardiac thrombi (*F. immitis* of dogs). The lesions due to adults of *F. bancrofti* are not well understood and may perhaps be referred to concomitant bacterial infections.

It is not improbable that the increase beyond a certain number in any species of free-living animals, large or small, which causes crowding and reduces the food supply is

brought to a standstill and the number reduced by superinfection with animal parasites perhaps as much as with bacteria and ultramicroscopic forms. Entomologists have long been acquainted with an automatic regulation of certain insect pests by parasitism. The observation of similar phenomena among higher animals is made impossible in nature because such weakened animals are destroyed by other agencies before the number reaches the necessary level to arouse attention. Only in artificial breeding places for small animals do we witness the appearance of numerous plagues which indicate that the absolutely non-parasitized animal is a rarity.

The transmission from host to host is incumbent upon all parasites. The host may die and with him most of the parasites known to us would perish, unless a transfer be effected by some artificial act of man. Hence some automatically adjustable mechanism must be in operation for the transmission of parasites from the body of one host to that of another during the life of the former. We might conceive of parasites as invading their respective hosts, destroying life and continuing multiplication upon and in the dead tissues, thence dissemination following the disintegration of the host body. Such a course is conceivable but not established among bacteria, although among certain parasitic fungi it is known to exist. Even the virulent anthrax bacillus, which might admirably fit into this scheme, is unable to sporulate except in contact with air. It is well known that anthrax bacilli are frequently missed entirely in the attempt to isolate them from putrefying bodies. The demand on most microbes to adapt themselves to both living and dead tissues is evidently too great. In the living animal they may be supreme while hosts of other bacteria are kept out, but in the dead body they must retire before this same host of putrefactive species.

The transfer of parasites from host to host is furthermore made necessary by a continually changing attitude of the host. The multiplication of parasites within the tissues of the host induces certain reactions in virtue of which they become more and more antagonistic to the parasites until complete destruction or at least cessation of multiplication has been effected. This transformation of the host known as immunization compels the parasite sooner or later to seek another host whose tissues are still unmodified. The transmission of parasites from one host to another is either definitely dependent upon certain animate or inanimate vehicles or else may take place in a variety of different ways. In any case the means of transportation or the vehicle must fit the mode of entry or the portal; otherwise an invasion is not possible. If the invasion occurs only by means of a certain insect, the absence of such insect prevents the parasite from getting a foothold in another host and the disease it may call forth fails to appear. If the invasion occurs through the inspired air, the parasite or its reproductive forms must first be suspended in air. Not only must the parasite enter the body of the host in a certain vehicle and through a definite portal but it must also be in a given stage of development. It must be ripe for the transfer. The difference in the environment of the parasite while in its host and during its usually passive migration is in most cases very great and special devices have been evolved to protect the life of the parasite. The passage from host to host which among intestinal parasites is preceded by the formation of eggs is characterized by the appearance of sexual elements or gametes among malarial organisms. The oocyst of coccidia becomes enclosed by a resistant shell. Only a few parasites undergo further development outside of the body in their protecting envelope. Among these are the eggs of such roundworms as *Ascaris* and *Trichuris,* the oocyst of certain coccidia, and the larvae of the hookworm. This ripen-

ing of eggs in the soil may have suggested to Pettenkofer his once famous theory of the ripening of the bacteria of cholera and typhoid in the soil, whereby they again acquire infectiousness after having lost this property in the body. Nothing appears to remain of Pettenkofer's hypothesis but its opposite. We would say today that the genuine pathogenic bacteria escaping into the soil, die sooner or later. Bacteria are evidently adjusted to prompt transfer from host to host, for there is no good evidence that they are provided with special protecting envelopes in their passive journey. One might suppose that the spore state would be admirably adapted for the temporary life in the open but only a few bacteria which come within the horizon of the medical bacteriologist produce spores. The more highly parasitic bacteria, such as the tubercle and the leprosy bacillus, do not have any unusually resistant stage. In general the resistance to destruction presented by pathogenic types is pretty much the same whether they are taken from tissues, from secretions or excretions, or from cultures. Certain species are uniformly more vulnerable than others. The resistance presented by bacteria in transit is probably due to the enveloping mass of mucus, tissue detritus, or albuminous (serous) fluids accompanying them outward. Experiments made to determine resistance to drying have shown for many species that the bacteria contained in secretions and excretions remain alive when dried longer than those from artificial cultures. The subject is very difficult to approach by experimental methods owing to the many contaminating saprophytic species which accompany pathogenic types outward from the body, as well as to the difficulty of determining whether bacteria are dead. The unmodified bacterium as it comes from the diseased or convalescent body without passage through cultures still awaits thorough investigation. So far as is known, the transmission of pathogenic bacteria is not dependent upon special insect carriers. They

are transferred chiefly by direct contact or by such vehicles as food, air, water, and inanimate or animate objects which become accidentally contaminated with secretions and discharges and which act as passive conveyors of the infection from host to host. In the exceptional case of the bubonic plague the rat flea is regarded as the chief vehicle of the bacilli from rat to rat and from rat to man. But even here the infection occurs through the more or less accidental entry of the highly virulent bacilli discharged from the intestine of the flea into the wound made by the latter in its attempt to get nourishment.

The absence of special intermediate hosts or carriers for the bacteria and many ultramicroscopic viruses suggests that diseases due to them may have depended largely upon the abandonment of instinctive protective measures and the huddling together of primitive man following increasing density of the population. If this be so, there comes the hope that such diseases may eventually disappear when civilization has reached a level to be established by sanitary science which would fully replace the loss of primitive instincts with regard to cleanliness. At present the countermovements of congested poverty in cities and industrialism are putting off indefinitely the realization of this hope.

We may summarize this chapter by the statement that the phenomenon of parasitism as it concerns the higher animals in its broadest aspects, as based on the fundamental demand of living things for subsistence, on the doctrine of fortuitous variation and mutation, with fixation by natural selection of those characters most useful to the parasite in the maintenance of the species, presents four different phases. It implies adjustment and adaptation to invasion, to multiplication, to emigration or passive discharge, and to transfer to fresh hosts. Each of these phases requires its own special machinery. The necessity for multiplying and for the progeny to leave the host

eventually results in the selection of loci of multiplication in cavities or tissues in more or less direct communication with the exterior. Even in the group of parasites which are transferred by insects and other ectoparasites from blood to blood, this need is complied with by residence in the peripheral circulation. These four fundamental demands of parasitism are met in a great variety of ways. Every parasite has solved the difficulty in accordance with its capacities which it received from its free-living ancestors as matched against the resisting powers of the host.

III

ABERRANT PARASITISM AND INCOMPLETE CYCLES

ALTHOUGH the four stages I have described must be successfully passed through by all invasive organisms, the strict limitation of the parasite to one host species, to a definite portal of entry and exit and to a well defined locus in the body is characteristic only of highly specialized groups of parasites. To overlook the many variations from this type would be to ignore important and difficult medical problems and to pass by what may be regarded as a possible route in the evolution of states of parasitism. The instructiveness of biological research lies as much in tracing deviations from a doctrine or principle as in the generalizations leading to the principle itself. The science of living things knows no sharp contrasts or open gaps. Transitions lead gradually from one formulated law to another. Modifications of well known processes occur on all sides. The subject of aberrant parasitism is of great interest in the study of disease, since a highly specialized parasite with a definite cycle tends to do little harm whereas in the process of straying into new hosts most serious and fatal diseases may have their origin. Biologically the most effective factor in the evolution of parasitism on the one hand is the continued life of the host; an effective factor in its suppression is the premature death of the host. Disease due to the parasite even if it does not end in the death of the host may affect the status of the parasite insofar as it may make the host an easier prey to other enemies for the time being. Otherwise the production of a disease

state in the host from which recovery always takes place does not count towards restricting or suppressing the parasite. In smallpox, a highly specialized form of disease, the parasitic invader rarely causes death unless associated with or followed by common infectious agents like streptococci.

In a discussion of aberrant parasitism we are confronted by a variety of possible conditions controlling it, of which only the most prominent may be considered here. In the first place it may happen that some host presents conditions for parasitism very similar to or even identical with those in the original host. The opportunities for testing possibilities of this kind are furnished by the huge army of offspring shed by many parasites. Dissemination in all directions makes association with many different animals possible. Furthermore, parasites being in various stages of adaptation to any given host may still possess undeveloped, latent capacities and such as have not been completely suppressed or lost. Conditions in another host may enable them to get the necessary start. These two factors, latent capacities for adaptation and opportunity to try them in many hosts, are responsible (1) for the occurrence of many instances of strayed or aberrant parasitism which are relatively transient phenomena, (2) for the existence of multiple hosts, and (3) for the final appearance of relatively stable so-called physiological varieties or races of parasites.

The occurrence of aberrant parasitism was to the parasitologist what the occurrence of variation in myology and neurology and angiology is to the anatomist. To find and describe parasites out of place furnished occupation and stimulation in the stage of the systematic study and description of parasites before the development of means for experimental and analytic inquiry. The consequence is that a large literature has grown up around aberrant parasitism of the larger forms. We must assume that this ephemeral parasitism is due either to

a very unusual concatenation of favorable circumstances, and therefore occurring only rarely, or else that the beginnings of a parasitic relation occur more frequently but are not observed because the parasitic cycle remains uncompleted or is prematurely destroyed. When the conditions in the aberrant host are favorable throughout and the cycle can complete itself we have then the phenomenon of multiple hosts. It is obvious that a sharp line cannot be drawn between aberrant and genuine parasitism until each case of aberrant parasitism has been given the opportunity under suitably controlled conditions to complete its cycle. A definition of a parasite with multiple hosts would be one which can maintain itself indefinitely by means of one host if the others were nonexistent. Aberrant parasitism, on the other hand, would comprise those excursions of a parasite which usually lead to its own death.

Among higher parasites with multiple hosts may be mentioned *Trichenella spiralis* which lives both in the rat and the pig. It may successfully invade and encyst in a variety of hosts and pass from one to the other. All that is necessary is that these hosts be cannibals to become true hosts. Even such a highly organized tapeworm as *T. echinococcus* may develop its larval stage in cattle, swine, sheep, and man. The final sexual stage may live in the wolf as well as the dog. So the larval or cysticercus stage *Taenia solium* normally in the pig may successfully develop in several other animal species and in man. In the human species it has been encountered in many organs, among them the eye and the fourth ventricle of the brain where the rupture of the cyst has caused instant death. Coming to the lower groups of parasites, the protozoa, bacteria, and ultramicroscopic forms, we find the experimental method used more extensively and successfully here in discovering new hosts. We must distinguish between the capacity of a host to respond to natural invasion and to artificial inoculation. A parasite may be made to multiply in a

foreign host if introduced artificially. The natural routes may be circumvented or the normal resistance broken down by large doses of the infecting agent, or both methods may be used simultaneously. The question still remains whether the microorganism could have successfully completed its cycle if left to natural agencies, or perhaps more to such agencies which are continually operative, whether natural or under human control. Among the parasitic protozoa the sexual cycle seems to be a steadying and controlling agency which restricts aberrancy. A. Negri infected guinea pigs with the sarcosporidium of the rat. Two spontaneous cases in man have been demonstrated, one by S. T. Darling. R. Erdmann was able to transmit the sarcosporidium of sheep to mice. It is of interest to note that the experimental infection of foreign hosts did not lead to any appreciable reaction on the part of the invaded muscle fiber, such as might have been anticipated. These successful experiments may, however, be a long way from the actual establishment of the parasite in a new host.

Among the red-corpuscle-inhabiting parasites, the piroplasms affecting large mammals have received much attention. They illustrate very well the phenomenon of race formation associated with an absolute host specificity following what was at some remote period an aberrant parasitism of some one ancestral species. The piroplasms of horses, sheep, dogs, and cattle have an undeniable relationship. All complete the sexual cycle in a tick as intermediate or definitive host. Even in the same host species, two varieties may exist. Thus in certain parts of Europe piroplasms are transmitted by *Ixodes ricinus,* while in our country *Boophilus annulatus* is the intermediate host. The European piroplasm (*P. divergens*) is clearly distinct from the American (*P. bigeminum*). Similarly two races or species have been found in horses, *P. caballi* and *Nuttallia equi.*

The flagellates known as trypanosomes are perhaps the most wandering and uncertain group among the parasitic forms. The early discoveries assigned the various trypanosomes to the respective host species in which they were found. They have been followed by important observations and experiments which have shown a plasticity and adaptability hardly to be equalled by the bacteria. This is all the more remarkable when we consider that these blood parasites with few exceptions are dependent on intermediate insect hosts for transmission, the restraining and eliminating and fixing influence of which on the parasite must be constantly at work. The relation of disease to the straying of parasites is very well illustrated by this large group. Thus *T. gambiense* is inoculable into a large series of animals in which serious and fatal disease is produced. It is probably an aberrant parasite in producing sleeping sickness in man, for its original hosts may be some wild animal as suggested by Nuttall. It has been recovered from cattle, monkeys, and dogs infected in the natural way by biting insects. The same phenomenon of aberrant parasitism has been observed in the study of *T. brucei,* the formidable trypanosome of domestic animals. It also is a relatively harmless parasite of certain wild animals. Certain trypanosomes infesting animals have become restricted to one host species and have lost any disturbing or pathogenic powers. Thus the rat parasite *T. lewisi,* the cattle parasite *T. theileri,* are non-fatal to their own or other hosts. A minute trypanosome found in cattle and which has been cultivated by Crawley and others is evidently harmless.

The capacity among trypanosomes for establishing themselves in more than one host is paralleled in some instances by a capacity to enter the host in several ways. Thus Nuttall states that *T. lewisi* may be introduced into its host by being fed in the dejecta of the infected flea or in the flea itself. It may be introduced through the wound made by the flea if

the wound becomes infected with flea dejecta. Among the pathogenic spirochaetes, experiments have demonstrated that monkeys may replace man as host of *S. duttoni*. The same spirochaete which in nature is transmitted by a tick (*Ornithodorus moubata*) has been transmitted to rats through the rat louse. In all these cases of successful transmission of protozoa to foreign hosts by inoculation or by the use of other than the usual insect or arachnid hosts, the final establishment of new parasitic relationships in nature if opportunities were at hand is suggested but not proved. The gap between the genuine and the aberrant host is probably very small in many of these newly demonstrated associations and a slight change in the natural environment, a slight shifting of temperature and moisture favorable to intermediate hosts, might lead to a new plague.

Within the miscellaneous group of ultramicroscopic organisms and those that will pass through bacteria-retaining filters we observe a relatively narrow host specificity. Thus practically no eruptive disease of man is shared by the lower animals. A limited inoculability appears to exist with some but there is no evidence at hand that animals may themselves perpetuate these infections. Among the same group affecting animals there is usually a single host for each microbe. Thus contagious pleuropneumonia of cattle, rinderpest, fowl pest, infectious pneumonia of horses, hog cholera (swine pest), sheeppox, attack but one host or at best only closely related varieties and breeds. There are two exceptions to this rule. Foot-and-mouth disease regularly attacks cattle, swine, and sheep. Rabies may be maintained by either wolf or dog and perhaps the cat. It is transmissible to a large number of other species, in which the further transmission owing to the absence of the habit of biting may and usually does fail.

Among the pathogenic bacteria, there is at present more or less confusion concerning intercommunicability because of

the use of inoculation which proves susceptibility under special conditions but does not necessarily establish a host relationship. Another reason for confusion is the existence of distinct races or varieties which maintain racial distinctions with much tenacity. In spite of the confusion still existing there are many well established facts illustrative of our theme. There is in the first place a group of human bacterial affections, including Asiatic cholera, typhoid, leprosy and syphilis, which is naturally restricted to man. In the case of all, the microorganisms may be forced to multiply in alien species by inoculation of large doses. There is no evidence, however, that any of these microorganisms could maintain itself in nature in any animal or that the organism would not become profoundly altered by repeated passages. Another group of diseases is the product of straying of such infections as bubonic plague, glanders, foot-and-mouth disease, anthrax, rabies, and paratyphoid towards the human subject. The question as to whether these infections might be perpetuated by man alone must be answered for each one separately and tentatively. Thus man has only a limited susceptibility to glanders, infection coming directly from the horse; otherwise there would be many cases among men. The same is true for foot-and-mouth disease. Anthrax might perhaps be maintained by the human disease alone provided the same disposal, or rather non-disposal, of dead bodies were the custom which obtains for domestic animals.

The most formidable instance of aberrant parasitism which has been elucidated by modern bacteriology is the bubonic plague. Coming from some original animal host as so-called reservoir and attacking the rat, the infection attacked man next on a large scale owing to certain deeply rooted customs and habits which favored the rat as a domestic animal. The pneumonic plague, far more formidable to man than the bubonic type, may have come directly from the original

animal host. It is not beyond the realm of probability that the bubonic plague virus may finally undergo such mitigation in the rat as to become harmless to man through one of those everyday processes of nature which demonstrate how events viewed as great by man may depend on very insignificant biological processes. Interest has been revived recently concerning a strayed parasitism known as rat-bite fever. The production of a paroxysmal febrile disease of the relapsing type by the bite of a rat was first studied in Japan, and later Japanese investigators described a spirochaete as the cause. The phenomenon is of interest since the human being is so susceptible. With the introduction of some regularly acting transmitting agent, a new disease might become established.

There is another group of bacteria, including staphylococci, streptococci, pneumococci, tubercle bacilli and paratyphoid bacilli, which do not appear very fastidious as to the host in which they vegetate. Here immunological data are of great value in sorting out races and in tracing them back to their primary host. When we look back over the past fifty years of work on the tubercle bacillus, we see how orderly facts range themselves when we have once accepted the doctrine that the true host invariably stamps its parasite with certain characteristics. Though the bovine tubercle bacillus strays from its true host in various directions the source of supply is always cattle. Should the pig which is very susceptible to the bovine bacillus give off the latter and infect other pigs we should after a time have a porcine variety differing more or less from the original bovine race. In the same way we should be able to sort out streptococci, paratyphoid bacilli, pneumococci, and even the colon bacilli, and by means of all the distinguishing tests at our command refer them back to their primary host or habitat, much as certain plants which have strayed from their original habitat and become disseminated over the whole globe and modified through the hands of man have been

traced back to their starting point. Referring parasites back to their original habitat may uncover unsuspected sources of infection and perhaps explain phenomena misinterpreted hitherto.

The only attitude consistent with science is the one which assumes that every difference in the functional characters of microorganisms otherwise indistinguishable has a definite significance to be cleared up. Differences in the agglutination characters of colon bacilli, of streptococci, of paratyphoid bacilli found in the same host species from time to time point to some specific but at present unknown host relation. Strains of a species closely adapted to a given host have almost invariably the same serological reactions no matter where found geographically, and whenever such serological reactions differ among strains, either the strains come from different hosts, or they normally inhabit different tissues of the same host, or else they belong to primarily different species of bacteria which have gained a close resemblance by loss of differential characters through parasitism. Only by rigidly adhering to such interpretation of the many slight differences found among seemingly identical strains may we hope to make progress towards a more thorough understanding of the influence of the host upon the physiological characters of parasites. A statement of Paul Ehrlich may be recalled here which is as true for biology as for the exact sciences: "In der Natur ist nichts spontan; alles hat seine Ursache."

Aberrant parasitism is of less importance to man than to closely related species of animals, since the animal associates of man which stand nearest to him and which might after a time exchange parasites with him are relatively rare in civilized countries today. The extent to which human tuberculosis affects monkeys is an indication of what might occur if we were surrounded by monkeys. Our domesticated animals, on the other hand, are zoologically so distant that very

few parasites have been interchanged with us. Among the lower animals, such as the birds, the case is quite different. There exists experimental evidence of the successful transmission of coccidia and other still undetermined protozoan parasites from one species to another. It raises the important question whether the steady decline of bird life may not be due in part to the infectious and parasitic diseases of our poultry yards transmitted to the casual visitor on the wing. The latter may then act as carrier and disseminate the acquired parasitism to other colonies of domesticated birds. It is furthermore probable that in some of these types of aberrant parasitism, the invader fails to complete its life-cycle in the new host. It may cause disease and even death but fail to become mature and to be discharged.

The many infectious diseases of the smaller experimental animals, such as rabbits, guinea pigs, mice, and rats, suggest a straying of infections from domestic animals or man. Thus the guinea pig is attacked by a pneumococcus, *B. bronchisepticus,* and *B. aerogenes lactis,* producing pneumonia; by paratyphoid bacilli and a streptococcus. All of these produce epidemics and they are therefore capable of maintaining themselves in this small host. It is highly improbable that the guinea pig brought these from its Peruvian home. Besides those mentioned there are several other infectious diseases found among guinea pigs which may be strayed parasites not yet fully domiciled in the new host. The possibility of inducing parasites to attack new host species has borne fruit in the hands of entomologists in checking the predatory activities of certain insects. Fantham and Porter have successfully infected a variety of hosts with *Nosema apis,* a microsporidian parasite of bees. This organism develops in the bee much as do coccidia producing asexual and sexual progenies, the latter assuming resistant spore forms. The cycle of the parasite was probably not completed in most of the aberrant hosts but

multiplication was observed in bumble bees, wasps, larvae of certain butterflies, in some diptera, and in the sheep louse.

In the years immediately preceding the introduction of bacteriological methods there was more or less discussion of the autochtonus origin of disease germs from filth. Thus Murchison regarded typhoid fever as originating *de novo* under unsanitary conditions which usually means the immediate presence of decomposing organic matter. Today we hear little of this old hypothesis. Translated into modern scientific language the *de novo* theory of the origin of infectious disease means the straying of free-living organisms into the body and multiplying therein. They would be accidental parasites endowed with aggressive powers which perhaps serve some other purpose in nature. Just how many infections and invasions which have become recognized are due originally to free-living organisms remains in doubt. There is one organism which may perhaps fit our scheme. It has been an almost continuous object of investigation for half a century. I refer to the anthrax bacillus. It is admirably endowed to maintain itself in nature through the capacity for the prompt formation of exceedingly resistant spores. Multiplying in a variety of organic infusions, even in a decoction of hay, it would seem as if it could get on without acting as a parasite of animal life. It is highly probable, though not demonstrable, that the anthrax bacillus is an accidental parasite. It lacks parasitic adaptation insofar as it is unable to sporulate in the living or dead tissues of the body. It is, moreover, the only spore-bearing bacillus which can enter through insignificant wounds. Watson Cheyne and others showed that a single bacillus inoculated into a guinea pig would prove fatal. Other spore-bearers that are known to multiply in the body, the bacillus of black quarter, of malignant edema, *Bacillus welchii,* and *Bacillus tetani,* all require either a large wound or some cooperating organism or a special predisposing con-

dition for their multiplication. Again the anthrax bacillus is not known to be a mucous membrane parasite or an inhabitant of the intestines. All evidence, in short, points to the exogenic nature of anthrax, favored, to be sure, but not dependent on parasitism for its multiplication and dissemination. There is no evidence that some progenitor of the anthrax bacillus has become a facultative or true parasite. The bacillus is not resistant to drying and is evidently less vigorous than the typhoid and paratyphoid bacilli. This weakness of the vegetative stage may have interfered with a parasitic evolution. The habit of spore formation of no use in the parasitic state has protected the bacillus in its free-living state.

Another organism, *Actinomyces,* makes a great leap from the stage of parasitism on plants to the human and animal body. Bostroem and subsequent investigators refer this fungus to vegetation as its true habitat. Occasionally it invades animals and may appear even in epizootic proportions, but it is always enzootic, tied to localities, just as the anthrax bacillus fastens itself upon the soil and remains there when once introduced. The actinomyces fungus has not been accused of passing from animal to animal or from animal to man or the reverse. The fungus is acquired directly from vegetation. Its capacity for growth and multiplication in the tissues, of burrowing even through bony structures and destroying them, is striking.

As bearing upon the question of the ancestors of the bacteria—whether coming from higher forms through elimination of sexual reproduction or from unicellular forms—it would be of interest to shorten artificially the cycle of certain parasites. It is known that malaria can be transferred artificially in the blood without the mosquito. The same is true of piroplasmosis. The injection of the blood of Texas fever from animal to animal would eliminate the sexual cycle and unduly stimulate schizogonic multiplication. Under such con-

ditions the parasite might eventually lose its adaptation to the tick and the sporogonic cycle would drop out, provided of course other concomitant changes did not destroy the parasite in the meantime. Similarly it is conceivable that coccidiosis among rabbits might be maintained by injecting the intestinal contents containing merozoites directly into the duodenum of a fresh host and continuing this procedure for a time. The oocyst would play no part since it must develop outside the host until the contained sporozoites are fully formed. The artificial suppression of the sexual cycle might lead to its eventual disappearance. In nature the asexual progeny or trophozoites might of themselves carry on the cycle since they must be discharged in large numbers while endeavoring to gain a foothold in other epithelial cells. To pass from one host to another they must be resistant to bacterial decomposition products in the large intestine, to partial drying in the feces, and to the gastric juice in the next host. It is quite evident that the formation of resistant spore membranes is the only solution of the problem in sight and so far as we know all coccidia have maintained intact this stage of their life cycle.

The shortening of the life cycle of parasites artificially has been done for *Spirochaete duttoni* by Nuttall who reports successful passage by inoculation through a hundred mice in series. The same investigator has kept a strain of *T. brucei* alive by inoculation from animal to animal for fifteen years. Just what would happen if these strains of "undiminished virulence" were set free in some domestic animal subject to the bites of the normal transmitters would be a matter for speculation, for the continued asexual multiplication in the blood of a foreign host may have modified the protozoa enough to interfere with their life in the insect host.

The successful straying of parasites from the normal to a foreign host may or may not be fraught with serious conse-

quences to the second host. For all parasites it will depend among other things on the number of invaders, that is, on the quantity of infection or the dose. For those parasites which multiply asexually—and this would include all protozoa, bacteria, and ultramicroscopic organisms—the fate of the foreign host depends upon whether this stage is largely suppressed, or whether owing to lack of resistance it is, so to speak, let loose in the new host.

Besides the straying of parasites from one host species to another there is a kind which is of great importance to medical science. I refer to the straying of parasites within the host from normal routes. It may be asked: Do we know when such deviation occurs? Are we sufficiently acquainted with the normal path, the normal loci of growth and multiplication? With the animal parasites, including the protozoa, the answer is not so difficult. Since we know in many cases the precise tissues and structures where they continue their development we may infer that if parasites are transported in the blood and carried passively everywhere, they are suppressed and destroyed except in the tissues where their multiplication takes place. *Trichinella spiralis* sends her progeny into the lymph current of the intestinal villi whence they reach the circulation and are carried passively to the skeletal muscles where they actively enter a muscle fiber. C. Frothingham described a fatal human case in which the larvae were found breaking out of the vessels in the liver, pancreas, brain, heart, and lungs. Romanovitch found larvae in pleural, subpleural, pericardial, and peritoneal cavities. They may bore their way out from capillaries of the heart and lungs into the serous cavities. These larvae may be considered lost since they have missed their final destination. Other parasites are similarly carried by the blood into all parts of the body but the final destination may be and usually is a very restricted tissue or a single organ. Sarcosporidia are, like the trichinae, des-

tined for skeletal muscles. The larvae of certain tapeworms, such as *Cysticercus bovis*, are found only in a few sets of muscles. *Klossiella muris,* a coccidium of the mouse which enters with the food, develops only in the epithelium of Bowman's capsule and the convoluted tubules of the kidneys. Some tropism or chemotactic influence is probably at work to direct the parasite to its specific tissue cell but this influence can scarcely come into play until the parasite has reached the tissue passively by way of the blood stream. Leiper and Atkinson in a description of their work on *Schistosonum japonicum* found that the miracidium or larva after escaping from the ovum in water was strongly attracted to a certain species of snail among others. In this snail subsequent developmental stages leading to the young fluke were found.

When we come to the pathogenic bacteria it may seem strange to consider them as straying within the body, for we are accustomed to meeting them anywhere. Yet bacteria are subject to the laws that govern protozoa within the host. Straying from the normal route means the destruction of the strayed organism, either during the life of the host, or after his death through inability to leave the body. We may assume without much contradiction that there is a route through the body which is most effective in discharging outward the largest number of an infecting progeny. This may be called a normal route. If in following this route the progeny acquires any special characteristic this will be selectively fixed. This route may, however, be so overlaid and masked by variations in the resistance of the host, by accompanying infections, by injuries, etc., that it rarely is mapped out clearly and thus remains unrecognized. It is, however, essential that the routes of infectious organisms from entrance to exit be mapped out so that deviations may be more easily recognized and their significance investigated. Thus in Asiatic cholera the locus of infection is the digestive tract. Any straying of the parasite

from the intestines is followed by destruction. In typhoid fever the route is not so plainly mapped out. The appearance of the bacillus in the blood is of no special use to the parasite except insofar as a wider infection of the lymphatic tissues of the intestines is favored thereby, for it is from this tissue that shedding outward takes place. We do not know whether entrance into the blood stream is necessary to carry the bacilli around the stomach. If so, entrance into the tissues would have to take place in the mouth or throat. The circumvention of the stomach is also made possible through the blood by discharge through the liver into the bile. Doubt exists also about the nature of the earliest multiplication of the bacilli. Do they multiply in the contents of the intestine and thence enter through any wounds or other defects into the blood and lymph stream? Or is their multiplication wholly restricted to lesions where a food supply is at hand which contains more nutritive or specific elements? Is the normal flora inimical to multiplication and is the modified or pathological flora incidental to the diseased state more favorable to multiplication at large in the lumen towards the end of the clinical disease? Putting these questions aside as not being definitely settled, it may be reasonably claimed that the digestive tract and its walls are the chief seat of the activities of the typhoid bacillus and that incursions into the blood serve only to make these activities secure. The entrance into the blood may or may not be considered an aberrant movement for the interpretation depends on the action of the stomach. Most of the bacilli are lost by this incursion into the blood and only those locating and multiplying in the lymphoid tissue of the intestine or those excreted in the bile or urine survive. Kolle and Hetsch maintain that, "We no longer regard typhoid fever as an intestinal disease but primarily as a bacteriemia." It would be fortunate if it were only such. As long as the disagreeable results of intestinal localization, such as hemor-

rhage, perforation, and secondary infection, remain, the disease is mainly intestinal. Moreover it could not continue without the intestinal localization. If typhoid ever becomes changed in type, it will be towards more intestinal localization and less bacteriemia. Incursion into the blood favors excretion through the kidneys and multiplication in the urine. To what extent this path may become a frequent one will depend partly on the integrity and resistance of the kidney and certain habits and customs of man. What will probably happen is the perpetuation of both fecal and urinary types of bacilli through the opportunities afforded by dense populations, provided the urinary type does not lose capacity for entry.

Taking next a different type of organism, the tubercle bacillus, we may state with some degree of certainty that the normal path of this organism as evolved in civilized countries, where the infection has existed for an indefinite period of time, is into the lungs with the inspired air and thence outward in the sputum after multiplication and destruction of lung tissue. All other paths are more or less uncertain. Notably the invasion of lymph nodes, unless associated with generalization and subsequent localization in some organs facilitating discharge outward, is destructive to the invader. The bovine race of tubercle bacillus produces in man types of infection departing from the normal human type. These strayed bacilli are lost, with rare exceptions. Only a fraction of one per cent of cases of lung disease are associated with the bovine bacillus. The behavior of the virus of leprosy and of syphilis still await satisfactory interpretation. A careful study of the investigations does not permit anything more than speculation as to what may be regarded as average or normal movements and what aberrant excursions or incursions of the respective microorganisms of these unique diseases. In the exanthematous diseases clinical medicine has

established what might be regarded as a normal course because of the characteristic skin reactions, in spite of the fact that the infecting agents remain unknown. Healthy carriers are not known in smallpox, measles, and chickenpox, probably because of the nature of the etiological agents, the well developed cycle, from respiratory tract to skin, and the arrangement for a copious discharge of the infecting agent at the termination of the disease. It is highly probable that the skin is the chief avenue of exit for the eruptive diseases. Aberrant movements of the virus if they exist are masked by concomitant infections. Everything points to the high antiquity of these affections.

Perhaps the most important locus or habitat of certain pathogenic bacteria are the mucous membranes. In the upper respiratory tract may be found the hemophilic bacteria, diphtheria bacilli, streptococci, staphylococci, and pneumococci. In the small and large intestines, chiefly the latter, colon bacilli, streptococci, *Proteus vulgaris, B. pyocyaneus,* the bacilli of tetanus and malignant edema, *B. welchii, B. necroseos,* and paratyphoid bacilli have been found. In the genital tract the microorganisms of venereal and suppurative affections find lodgment. Among domestic animals the group of bacilli known as *Septicaemia hemorrhagica* or bipolar organisms, which are frequently associated with pneumonic affections, are localized on the mucous membrane of the throat. From these various situations excursions or incursions into the adjacent structures, the lymph nodes and the blood are made, producing certain well known diseases. In pneumonia the incursion into the blood is in a sense a straying from the beaten path. This incursion when it does occur probably leads either to the destruction or internment of the pneumococci or to death of the host. In any case it is to the parasite neither a necessary nor a favorable movement. Even the incursion into

the lung tissue itself is aberrant for certain groups of pneumococci which maintain themselves indefinitely in the throat.

The very thorough and illuminating researches of Flexner and his coworkers in infantile paralysis have pretty conclusively ranged the etiological agent of this disease as a mucous-membrane parasite with incursions into the central nervous system. It is by no means clear just what advantage the virus derives from this movement unless in some way it returns to the upper respiratory tract. That it may be accidental is suggested by the many abortive forms and the general high degree of resistance in the population. If it multiplies on the mucous membranes return is unnecessary. As a rule invasion is easier than return by the same route. Invasion is accomplished before the host reacts. A similar situation is presented by the meningococcus. The probability that the invasion of the central nervous system is aberrant is suggested by the fact that this coccus presents the largest percentage of healthy carriers of any disease. The microorganism is thus amply cared for, even when not causing disease. It remains for the future to define more accurately and explicitly the relation which these mucous-membrane parasites bear to the membrane itself and to determine more clearly the etiological moments which cause multiplication and invasion of the tissues in one case and not in another, or which delay or precipitate such multiplication and invasion.

Bearing in mind the many different glandular structures of the mucous membranes, the different functions of the various tracts, we may conceive of a multiplicity of localizations of microorganisms, each differing from the other and affording for the many transient species passing through the body opportunities for settling down. Many of the bacteria encountered are not cultivable by ordinary means. The special habitat of intestinal species remains in doubt. We make no distinction between the miscellaneous contents of the large

intestine, for instance, and of the tubules and larger flask-shaped recesses bathed in mucus, as loci for different species. Nor do we take into account the great difference in the food values of these loci for developing invasive species of bacteria. More than these possibilities are those afforded by mucous membranes which have lost normal tone and which may be constantly discharging even in traces, lymph, plasma, or serum and leucocytes together with desquamating cells. In this medium bathing the membrane, bacteria might multiply and prepare themselves for an incursion into the blood and lymph stream, since the food supply differs but little from that on the other side of the membrane. Such bacteria might be relatively harmless to their immediate host carrier but they might be virulent for others to whom they are accidentally transferred. Through such training on defective mucous membranes, microorganisms may reach a higher degree of invasiveness or virulence after several rapid passages. Coming upon fresh mucous membranes especially in certain seasons when abnormal states are the rule an epidemic associated with incursions into air tubes, lungs, lymph nodes, ears, etc., may arise apparently *de novo* and gain great headway in a short time.

It may be claimed that organisms which are steadily driven out of the blood and tissues by immune reactions and which maintain a precarious existence on the mucous membranes are not to be counted with genuine parasites but are simply predatory organisms differing but little from their relatives in decomposing organic matter. The decision must rest with the habitat. If these microorganisms have some habitat in organic matter whence the mucous membranes recruit their stock the claim would be good. But there is no evidence which points to any habitat other than the mucous membrane or which indicates that they can survive the struggle with the flora of decomposing organic matter. Their adapta-

tion has gone so far that it even restricts them to the mucous membranes of certain species. Some are even limited in their food supply, as for instance the hemophilic bacteria which thrive only when blood or hemoglobin is available.

The subject of aberrant movements of parasites within the host, of excursions from recognized habitats, of multiplication in distant organs is bound up with the phenomenon of specific susceptibility and resistance of host and parasite respectively. The subject is of most interest to the pathologist and clinician who is being continually confronted with departures from the type. It is here that the physician enters when he describes clinical variations as does the anatomist, structural variations. To the parasitologist aberrant parasitism presents its chief interest in the possibility that man himself may at times and unwittingly complete the cycle of an incomplete aberrant parasitism through his own activities. By bringing together patients, the physician of a former century, ignorant of asepsis, made himself the vehicle for puerperal fever, erysipelas, and other septic infections. But in a larger way man may become instrumental in introducing an aberrant parasitism and perpetuating it as a new disease. Advancing civilization with its ever increasing intensity of intercourse between widely separated territories, its artificial relationships between individuals constantly shifting through changes in customs, not only bring different races of human beings together but cause a similar change of relationship among animals and among plants, between animals and plants and between these and man. That the possibilities involved in this continual active and passive intermingling of hosts and potential parasites have been exhausted is not at all likely and the appearance of hitherto unknown combinations of host and parasite need not surprise us.

Aberrant movements are, on the whole, the most important factors in parasitism and in the diseases due to it. Aberrancy

is the adventurous element in the life of the parasite, which leads either to death or to new conquests. Establishment in new hosts paves the way for the formation of new races and varieties, for the new host modifies and molds the invader until a new equilibrium has been established. Aberrancy of parasites is furthermore responsible for much disease whenever they reach a more yielding host. This is almost the rule among protozoan forms. Most epidemics or pandemics are probably due to strayed parasites. A study of epizootics among small experimental animals kept together in large numbers tend to show that such diseases are most virulent at the start and gradually change their characters, becoming less infectious, more chronic, non-fatal, and topographically altered as regards the incidence of lesions. The epidemic is probably the first sign of a straying of parasites from either near or more distantly related hosts or from an immune group to a susceptible group of the same species or race.

IV

THE STAGE OF CONFLICT BETWEEN HOST AND PARASITE

IN THE preceding pages there have been defined parasitism as an evolution from predation, the cycles which all established parasites must follow as well as the more or less accidental aberrations from such cycles and their consequences. Of the four stages of any cycle, the one which involves the multiplication of parasites within the host is of prime importance to the host and essential as well to the parasite. It is the one in which the conflict between host and parasite centers. It is the stage to which medical science has given most attention, and it is the one in which disease as well as cure from disease is generated. As a result of the pressure upon medical science to combat this stage which deals with the practical issues of saving life and preventing disease, research has moved in whirls or waves rather than in a continuous stream. The force of these waves is plainly visible in the literature of medical science. With the phenomenal success of Pasteur in the development of a method for the control of anthrax by vaccination came a period largely given up to the search for vaccines. With the discovery of a soluble diphtheria toxin by Roux attention was turned aside to discover a toxin in all microorganisms. The announcement of tuberculin as a cure started a wave of bacteriotherapy, while the closely following discovery of antitoxins led some to try to find an antibody even to alcoholism. Later the discovery of opsonizing substances led among other things to the habilitation of phagocytosis which, although in the field for nearly twenty years,

had not up to this time received due recognition. More recently the discovery of anaphylaxis overshadowed earlier issues and threatened to dominate all other views concerning the nature of infectious diseases. Today ultravisible organisms have their day and the mysterious bacteriophage is in the foreground of experimental bacteriology. These fundamental discoveries with the partisanship roused by them simply demonstrate the intricacy of the problem before us. The line of thought followed here in attempting to construct a scheme representing the relation between parasite and host has already been outlined. It is drawn from the larger everyday phenomena of nature representing the struggle for existence. The primary energy of living things is expended as we see it on the surface in the search for food. In this search every species is provided with means, usually denominated weapons and means of protection, since the search for food brings animals into conflict with one another. The food is obtained largely by destroying weaker species and consuming them. This, in substance, is the relation of animals to other animals and to plants. This quest for food has developed the almost universal predatory habits of animals. It has at the same time developed the necessity for self-protection on the part of the species attacked. Since all species of animals are exposed to attack at one time or another, weapons both for offense and defense, for aggression and self-protection are possessed by all in varying degree. The same weapons may serve both purposes or very different devices may be used by the individual. Thus the animal which feigns death at the approach of a stronger enemy may fiercely attack the weaker prey. That unicellular animals may have what appear to be defensive weapons is indicated in studies by Mast on the attack of one ciliate (*Didinium nasutum*) on another (*Paramecium*). *Paramecium* after being attacked responds by discharging a great number of so-called trichocysts from the ectosarc for

some distance around the point of injury. As soon as trichocysts come in contact with water they form a mass which appears to have a jelly-like consistency, and the increase of this mass due to the extension of the trichocysts forces the two creatures apart. The result of the contest depends on the relative size of the protozoa in the struggle. Similar conditions obtain in parasitism. Not only are there many stages of transition among parasites from the purely predatory to the purely parasitic habit, but parasitism itself may be considered as a continuous warfare on a subdued scale in which offensive and defensive weapons are in action. In attempting to present actual data and examine this theory in the light such data may shed, I am endeavoring to put myself in line with the activities of living things rather than with the natural or artificial fragments into which we may dissect them. In this analysis bacteriology has blazed the way and most of what we know today is derived from it and its offspring, immunology. Before a survey of this relationship is attempted, certain broad easily demonstrable facts should be placed in the foreground.

The study of animal diseases has shown that host species differ among themselves in their susceptibility to parasites. Some species offer definite unbreakable resistance to parasites which readily multiply in other species. There are bacteria which will kill an ox and leave the house mouse untouched. What are highly dangerous to one species may be harmless to other even nearly related species. Higher animals entirely immune to all known pathogenic bacteria do not exist. In individuals living in territories where certain diseases are not endemic and moving into those where they prevail, certain parasites tend to multiply with such unrestrained rapidity consistent with their cycle that the life of the host is endangered. This is true of human malaria as well as of piroplasmosis in cattle. In both groups of diseases the red blood

corpuscles are attacked. Multiplication may be checked only by death or lack of normal corpuscles. Such diseases resemble true septicemias. In endemic territories where the parasite has been at work during indefinite periods and upon many generations the disease is more like a harmless parasitism. It appears only sporadically, is mild, non-fatal and set in motion usually by other causes. In malarial territories of Africa, Koch found the disease chiefly a children's disease, running a relatively mild course. More recently Macfarlane studied a small European settlement in Portuguese East Africa. "One of the most remarkable points brought out by the examination, is the very large numbers of parasites which these native children are able, through the gradual development of immunity, to harbor in their blood without apparent symptoms. In one or two cases, parasites were present to the extent of two or three to every field of the microscope, and one to every two or three fields was fairly common. In Europeans, in Central Africa, such large numbers are very uncommon in my experience. Symptoms in them are produced by much smaller numbers, and quinine treatment checks multiplication before it proceeds much further. It should be noted, nevertheless, that most native children suffer from malaria, from time to time, and the mortality among them from the malignant form is probably great." Macfarlane found malarial parasites in the blood of 72 children, or 85.7 per cent of the total number. An enlarged spleen was found in 61 children, or 72.6 per cent of the total. Positive evidence of malaria was found in 94.04 per cent of the total.

The pathogenic trypanosomes living free in the blood present the same problems suggested by the multiplicative stage of the parasites which invade the red corpuscles. Here also there are resistant host species acting as so-called reservoirs of the parasites and non-resisting individuals of the same species coming from regions outside the enzootic areas. In

other words, the hosts in endemic regions are much less liable to succumb, and recover more speedily.

Irrespective of the endemicity of any given disease certain races possess a resistance traceable to genetic influences and not due to endemically produced resistance. Even in the same race, there are immune, highly susceptible, and partially susceptible individuals. It has been customary to class those species and races which are highly resistant to certain types of parasitism as naturally immune and to consider those which are suspectible but which recover from disease processes incited by parasitism as having acquired immunity. Natural and acquired immunity are usually regarded as due to essentially different tissue states and activities. In other words, the differences are looked upon as qualitative rather than quantitative. All host species are completely resistant or immune to some form of infection or parasitism. Perhaps by taking an inventory of the various antagonistic processes between parasite and host as they have been brought to light we may be able to gauge more accurately to what factors complete immunity and high susceptibility are due. Underlying all host-parasite conflict is the universal function of digestion and assimilation in both host and parasite. The animal body is keyed to the process of making over and utilizing all alien substances entering the system. The digestive tract reduces ingested substances to harmless smaller fragments capable of being absorbed and later worked over. In parasitism, however, the digestive tract is circumvented and foreign substances, in the guise of protozoa, bacteria, larval worms and the like, enter the lymph and the blood and they must be digested or at least made harmless by agencies probably different from those active in the digestive tract.

As possible defensive agents physiologists and pathologists turned their attention to ferments or enzymes. It is not surprising that, in view of the powerfully disintegrating activity

of the digestive ferments, similar substances should have been looked for in the blood and tissues. Proteolytic ferments in blood and certain organs had been recognized since 1891. Thus a bit of kidney or spleen of the rabbit, dropped on 10 per cent gelatine can be seen to liquefy it slowly. Certain tissues placed upon sterile coagulated serum or egg will soften it in time. In 1892 Friedrich Mueller called attention to the liquefaction of pneumonic exudates by the invasion of leucocytes. The ferments of these cells were thoroughly studied by E. L. Opie in 1905 to 1907 and special attention given to differences between the ferments of the white blood corpuscles such as the polymorphonuclear cells and those of the lymphocytes and mononuclears. He also defined more definitely than had been done before the function of a certain anti-ferment of the blood and its bearing upon the dissolving action of purulent fluids. The relation between these enzymes and the mechanism by which the body resists invasion was not cleared up, and the evidence indicated that they did not come into play in this mechanism.

The importance of living leucocytes as sources of enzymes led to very industrious and painstaking studies of the effects of leucocyte extracts on bacteria. The work of Hiss, Kling, Zinsser, and others has shown that bactericidal agencies reside in extracts cautiously made in several different ways, but the activity is relatively slight. Ferments as protective agencies have been especially championed by Abderhalden. He has shown that the injection of foreign protein and carbohydrates is followed often within a few days by the appearance in the blood of the treated animal of ferments which act upon these substances and split them into simpler compounds. Abderhalden is inclined to attribute great importance to a prompt response of the tissues to the introduction of foreign matter in the struggle with infectious agents.

To the host activities mentioned should be added a variety of substances which may have aggressive or protective functions. Among them are the normal hemolysins dissolving the red corpuscles of certain alien host species and bactericidal substances. These bodies probably play a part in the aggressive activities of the host but this part is not clearly defined and must evidently be reinforced by other agencies in any successful action towards invasive bacteria. The contradictory evidence on the functions of bactericidal substances has been pointed out frequently since Behring first studied the bactericidal action of the rat's blood towards anthrax. In fact a study of the many reactions towards bacteria which occur in the blood serum of different animals and which are prototypes of the specific immune reactions following natural or induced disease has thus far led only to contradiction. Behring and Nissen pointed out many years ago that the pneumococcus is not killed by the blood serum of the immune guinea pig, nor by serum of immunized rabbits; that the serum of the naturally immune rat destroys anthrax bacilli. The same is true of the serum of the highly susceptible rabbit. Again the serum of the naturally immune dog is not bactericidal towards anthrax bacilli. The serum of the guinea pig destroys cholera spirilla but not the related *Vibrio metschnikovi* until the host is immunized towards it. The same organism is not killed by the serum of the immune rat.

Distinct from any of the foregoing are two substances found in the normal blood of mammals, alexin or complement, and opsonin. The first mentioned substance, known only by its action and thermolability, is capable of causing certain destructive changes, such as the laking of red corpuscles, only after the cells have been exposed to a second substance in the blood, known as immune body, amboceptor or sensitizer, and developed during the immunizing process. Neither substance alone can operate successfully. Opsonin,

another substance known only by its activities and thermolability, is capable of preparing certain substances and bacteria exposed to it for active ingestion by polynuclear leucocytes. Such substances are not ingested without previous immersion in the opsonizing serum. The relation between alexin and opsonin is not yet fully clarified. Most authorities are inclined to regard them as distinct substances. Levaditi and coworkers found it difficult to dissociate opsonins from complement. The same difficulty was experienced by Muir and Martin.

That the host possesses certain normally active anti-alien destructive capacities is established by more general observations. One of the first striking things to impress early bacteriologists was the fact that of the myriads of microorganisms in the environment of the higher animals and of those which multiply in and which pass through the digestive tube only relatively few species gained entrance into the tissues and multiply therein. Even large numbers injected directly into the bloodstream disappeared. Some mechanism must therefore exist which wards off during life the hordes of species which attack the body after death. These early observations led to rather prolonged controversies on the so-called sterility of the normal body tissues. The tissues are not absolutely sterile. W. W. Ford showed that the liver and kidneys of rabbits, guinea pigs, dogs, and cats contained bacteria in over 75 per cent of the organs examined. In many instances spores of bacteria may be found which, ordinarily, fail to find conditions suitable for germination and multiplication.

The normal anti-alien activities may be thus classed as either destructive, bactericidal, or simply suppressive, or inhibitory. The conditions under which the latter work are not known. Even pathogenic species may be encountered in healthy animals. It is the lymph nodes draining given territories of the mucous membranes of lungs, digestive tract, uri-

nary tract, mammary gland, and genital tract, which are the first stopping places of these organisms. Here they are held and destroyed unless some depression of the host or injury to the tissues starts them into multiplication. Notably the mesenteric lymph nodes, draining the digestive tract, may contain them. The host tissues thus possess a practically unlimited destructive and inhibitory power over certain bacteria and more rarely a limited power over certain other forms. It is this capacity or incapacity to suppress or destroy which underlies the classification into pathogenic and nonpathogenic parasites.

Before discussing the changes observed in the host under the influence of a multiplying parasite within it, we need to sketch what is known of the aggressive and protective mechanisms of the parasites themselves. These may be assumed to vary from species to species, to differ widely in the large groups of worms, protozoa, and bacteria. The fundamental mechanism is probably the same and the variations built upon it are due to differences in host and parasite constitutions.

The discovery by Emile Roux in 1885 that diphtheria bacilli give out into the culture liquid in which they are multiplying certain poisons, called toxins, represents one of the milestones of progress in bacteriology. These substances are most easily demonstrated by passing through bacteria-proof filters the culture fluids in which bacteria have multiplied. They are known only by their properties. They have not yet been obtained in a pure state and their chemical composition remains unknown. That they are not living organisms nor ferments, is proven by their purely quantitative activity. A given dose injected into a susceptible animal, such as the guinea pig, produces an amount of injury closely correlated with the dose. Although soluble toxins, also known as exotoxins since they are shed into the culture liquid and do not

adhere to the organisms, have been searched for among many species of bacteria, they were found in relatively very few, among them in the tetanus and the botulism bacilli both known for their frequently disastrous activities. If exotoxins are so scarce, it was argued, perhaps the aggressive weapons of bacteria are locked up in them. Bacteria have been subjected to various destructive procedures to liberate the hypothetical endotoxins and a number of fairly toxic substances were obtained from typhoid, dysentery, and tubercle bacilli, from meningococci, and cholera vibrios. The action of endotoxins is best illustrated by Pfeiffer's experiments with the vibrio of Asiatic cholera. The normal guinea pig dissolves a certain number of vibrios injected into the peritoneal cavity. When the number reached a certain level all the vibrios may still be destroyed but the guinea pig succumbs to the liberated endotoxins. The significance of endotoxins as weapons is not clear. When many bacteria are injected the destruction of a portion in engaging and absorbing the aggressive activities of the host may protect the remaining bacteria. In natural infection, however, where the original dose is small and the infection started by very few organisms, such a mechanism cannot be of any avail. In the case of the guinea pig, the endotoxin would be of no use in protecting a few cholera vibrios injected into the peritoneal cavity, for they would be destroyed in any case until a lethal dose was injected. Perhaps the simplest view concerning endotoxins is to regard them as original constituents of the bacterial cell of no special or of only secondary significance to the bacteria since most free-living bacteria contain similar toxins. Concerning the significance of endotoxins as the chief weapons of bacteria, Professor W. H. Welch in his Huxley lecture in 1902 found it difficult to reconcile himself "to the doctrine that bacteria . . . do their chief injury to the body, not while they are lively and vigorous but

after they become corpses and in consequence set free their protoplasmic poisons."

Next to the toxins as promoters of bacterial multiplication the aggressins of Kruse and Bail have received most attention. The concept of an aggressin as distinct from a toxin was first formulated by Kruse and then developed experimentally by Bail and coworkers. If, according to Kruse, a salt solution suspension of dysentery bacilli be heated at 60°-65° C. and then the bacilli removed from the suspending fluid by filtration, the filtrate added to dysentery bacilli favors their multiplication in the body to such a degree that one-thousandth of the minimum infectious dose is still capable of multiplying in the peritoneal cavity of the guinea pig. In other words, the aggressin has increased the infectiousness a thousandfold. The twentieth part of the same extract halves the infectious dose. According to Kruse, the aggressivity of extracts of dysentery bacilli can be checked by immune serum whereas the toxicity remains.

Bail's original aggressins were prepared from exudates formed in body cavities after inoculation. These exudates freed from suspended matter and bacteria greatly favored bacterial infection by reducing the effective dose as was done by Kruse. They paralyze alexins, for when added to normally bactericidal serum the power to destroy bacteria is lost. Kruse regards aggressins as of limited specificity, Bail regards them as specific.

Another group of functions of bacteria, those concerned with metabolism, next claim our attention as possible offensive agents. Ferments acting upon coagulated blood serum, upon gelatin, and milk are widely distributed among bacteria. The same is true of intracellular ferments acting upon carbohydrates. An examination of both parasitic and nonparasitic species shows, however, that the latter are best endowed with these ferments. Although some of the former,

such as anthrax, Asiatic cholera, and staphylococci, liquefy gelatin and blood serum, such bacteria as streptococci, typhoid and paratyphoid, plague, and many others have no such capacity. Similarly the action on carbohydrates is most widespread among non-invasive bacteria. In the colon-typhoid group, the power to ferment sugars other than dextrose and a few other substances, such as mannite and maltose, is a pretty certain indication of absence of invasive power. In general we may say that among invasive species there is manifested a contraction of fermentative and proteolytic activities in culture media when compared with the physiological activities of saprophytic relatives. There is therefore no evidence favoring any direct association of fermentative and proteolytic activities in nutrient media with parasitic power.

The limited distribution of the aggressive, toxin-producing capacity naturally leads to a search for functions of resistance. These I would dominate, on the part of bacteria, protective or defensive. Their localization may be assumed to be in the outer zone or ectoplasm of the bacterial cell. Owing to its smallness the constitution of this cell remains a matter for speculation. Protection, however, may be conceived as residing in special secretory functions, whereby envelopes are formed. These actually exist among certain bacteria as mucous envelopes or capsules. There is, furthermore, protection possible in a limited permeability of the cell wall or ectoplasm, which would make capsular protection unnecessary. The theory of protective capsules has been a favorite one and a considerable body of literature has grown up around it. Notably the assumption of a capsule by the anthrax bacillus in the blood has been the theme of many writers. The presence of capsules in pneumococci whether derived from human or animal sources shows how strongly this species is wedded to this structure. Similarly certain streptococci, certain races of the bipolar group of *Septicemia hemorrhagica* and *Streptococcus*

mucosus are found with such envelopes in the body fluids. According to Toenniessen the capsule of the Friedländer bacillus is responsible for its pathogenic power. When this capsule has been removed by cultivation, the virulence sinks very low. Among protozoa, amebae encyst themselves very promptly for protection. Kurt Nägler discusses the formation of cysts as phenomena of adaptation due to environmental factors. Marine protozoa, according to Nägler, have not developed cysts because their use is not called for either as a protection against drying or as an adaptation to other conditions such as are met in the invasion by parasitic protozoa. In certain groups of bacteria, semiparasitic in character like *B. coli,* some races possess capsules which are readily lost in cultures. They represent the lowest grade of defensive adaptations. Among the products of saprophytic bacteria mucin-like substances are not uncommon. Such substances may perhaps be utilized by bacteria when a parasitic life is entered upon. Rettger has described such a substance. The bacilli of *Septicaemia hemorrhagica, B. bronchisepticus, B. fluorescens,* and glanders bacilli develop a viscid condition of the mass of bacteria in cultures. This is not present in the earliest cultures but appears after several generations, often so suddenly that some contamination of the cultures is at first suspected. The tubercle bacillus develops a distinctly viscid or sticky growth on egg media. Various writers have described viscid mucus-like varieties of the anthrax bacillus. This change the writer regarded as due to some transformation of the capsular substance whereby the latter, originally consistent and optically visible, became softer and no longer to be outlined around the organism. Overproduction of the mucous capsule may be seen now and then when certain strains of pneumococci produce spontaneous peritonitis in guinea pigs. The exudate then becomes syrupy and the microscope shows myriads of feebly

outlined bodies five to ten times the diameter of the contained pneumococci. Unless examined in water after staining, this phenomenon is apt to be overlooked. So striking and large are these capsuled organisms that for the moment they suggest some kind of protozoan parasite. Some years ago the writer observed the presence of a mucin-like envelope in cultures of *B. bronchisepticus,* which is precipitable with acetic acid. This substance is probably utilized by this bacillus in attaching itself and adhering to the cilia of the bronchial epithelium in various animals. The existence of substances of this kind makes it desirable to search for other unknown substances which may be of use to parasites in maintaining themselves in a hostile environment.

The capsule of the anthrax bacillus disappears in cultures but reappears in the susceptible animal body. Bacilli which fail to produce such capsules after inoculation fall a prey to certain host cells. The virulence of a culture thus depends upon the ability of anthrax bacilli in cultures to reassume the so-called "animal" state. In leprosy Babes has described a substance formed by the bacilli which collects in larger or smaller spheres, or else forms a cohesive binding material for the bacilli and even permeates certain cells and tissues in greater or lesser concentration. Danysz cultivated the anthrax bacillus in the serum of the naturally immune rat. It is well known that the serum of the rat destroys anthrax bacilli. By culturing the latter in bouillon and a little serum and increasing the latter gradually Danysz trained the bacilli to multiply in a stronger concentration of serum. They acquired thereby a thick mucilaginous sheath which absorbed the injuring or inhibiting substance in the serum in proportion to the virulence of the bacilli. If this inhibiting substance is abundant, in fastening itself upon the microorganism it interferes with assimilatory processes and permits the autolytic ferment in the bacilli to act upon and destroy them. In experiments de-

signed to immunize the anthrax bacillus to arsenic similar mucilaginous sheaths appeared. This substance overproduced, fixes the poison or antiseptic. Coagulation and arrest of functions take place and autolytic processes destroy the bacilli. It is probable that the so-called aggressins of bacteria described above are shed capsular material which engages and neutralizes the normal protective agencies of the blood.

Leaving the fragmentary information we possess of aggressive and protective capacities of parasites, we are now confronted with the problem, how the host reacts to them. The experiments of Behring and Kitasato in 1890 brought to light the remarkable fact that when modified toxins of the tetanus bacillus are cautiously introduced into the body of small animals and the dose gradually increased, something appears in the blood of the treated animal which, when mixed with the toxin, neutralizes its action. Within limits the neutralizing strength of the blood rises with continued treatment of the animal. A similar substance was demonstrated in the blood of animals treated with diphtheria toxin. This substance, known as antitoxin, is highly specific, neutralizing only the toxin which gives rise to it in the treated animal. Antitoxins have not been isolated from the blood serum as chemical entities; their existence is known only from their action upon toxins. The action of both is measurable in their effect on guinea pigs down to a thousandth of a cubic centimeter.

Soon after the discovery of antitoxins, other manifestations of reactions on the part of the invaded host were disclosed. The blood serum of the normal animal is indifferent to bacteria mixed with it. When such animal is inoculated repeatedly with living or dead bacteria, the blood serum acquires the property of clumping or agglutinating the same species of bacteria in dilutions increasing up to a certain maximum with the number of injections which the animal has received. This phenomenon is also highly specific and has

been of the greatest value in recognizing diseased conditions. Besides the agglutinins, the blood serum of immunized animals may also contain substances which cause precipitates with the culture fluid from which the bacteria have been removed by filtration. Furthermore, in such blood sera the complement or alexin, present also in normal blood, comes into play and is bound to the specific bacteria in the test tube, something which does not occur in normal blood serum. As already mentioned, a few species of bacteria are killed in immune blood sera, among them the cholera vibrio. Such sera contain bactericidal substances.

A peculiar reaction of the animal body, the relation of which to the immune reactions described is problematical, is known as anaphylaxis. The best illustration of this process is the effect following injection into the tissues of any animal blood serum from another species. Only a trace is required for the first injection. If after several weeks a second larger dose of the same serum is injected, the animal promptly becomes subject to violent spasmodic attacks which lead to death within a few minutes if the dose exceeds a certain minimum. A fresh animal treated in the same way shows no disturbance. Many variations of this phenomenon have been observed, all of which show the strong anti-alien behavior towards proteins of even closely related species. Nearly all proteins whether of animal or vegetable origin produce the same type of symptoms. Anaphylaxis is probably related to the reactions appearing in hay fever, asthma, and food idiosyncrasies. The fundamental explanation of these reactions remains to be made. They are perhaps best interpreted at present as a developing capacity of the injected animal of splitting the foreign protein into fragments which happen to be toxic to the animal itself. A further detoxication seems impossible. It is not to be denied that certain constituents of parasites may undergo similar disintegrations in the host and

that the resulting shock is masked because of its weakness. The well known tuberculin reaction belongs to this general class of phenomena. Its value depends on the fact that the tuberculous individual does not become immune to this substance but continues to react whenever this product of the tubercle bacillus is injected.

We have now briefly described a miscellaneous lot of phenomena and manifestations associated with bacterial invasion of the mammalian and avian body and we are confronted which the task of fitting them into some scheme which will interpret to us the several types of parasite-host relationship—the complete resistance, the complete susceptibility, and the many intergrades of recovery from the injuries following partial susceptibility. The first involves no multiplication of the parasites; the second, relatively unrestricted multiplication; and the third, temporary multiplication of various intensities.

Perhaps the most lucid method would be to concentrate our discussion on individual types of parasites about which scientific research has revolved for a half-century, collect the data that have stood the test of time, and formulate some theory consistent with each of them. We would then be able to assemble the various theories into some fundamental attitude of the body underlying all forms of parasitism. Such a procedure does not come within the scope of these pages. An attempt will, however, be made to frame, on the basis of a few illustrations, an underlying theory to be built upon or demolished by those prepared to gather together a fuller history of the host-parasite complex.

Among the lowest type of parasites the production of soluble toxins enables certain bacteria to gain a foothold. Only one among them—diphtheria—gives rise to a true infectious disease transmissible regularly from host to host. The remaining ones (botulism, tetanus, *B. chauvoei*) are accidental dis-

ease producers not transmissible in cycles from host to host. Any subsequent advance of these bacteria towards a parasitic existence depends on other qualifications not possessed by them. That diphtheria is a surface parasite and has no other means of maintaining itself or of invading the body is shown by the fact that it is entirely inhibited through the neutralization of its toxin by the developing antitoxin.

A somewhat different type of parasitism is presented by the vibrio of Asiatic cholera. This organism multiplies with great rapidity in the small intestines. If its multiplication surpasses a certain limit, the patient succumbs to a dehydrating process following general intoxication and injury of the intestinal mucosa. The theory of endotoxin poisoning has been mentioned as well as the fact that the blood of immune individuals is bactericidal. It would seem as if the vibrios were destroyed *pari passu* with multiplication. The destruction sets free the endotoxin. This injures or paralyzes the epithelial covering of the mucous membrane and is absorbed to injure the host system further. Only when the destructive process exercised by the host gains rapidly on multiplication is recovery possible. Complete immunity of the greater portion of the infected population is due to the prompt, early destruction of the entering vibrios.

A more advanced group of parasites comprises bacteria which are capable of invading the body tissues and by multiplication in many localities destroying life in a short time. These are the septicemic and pyemic organisms (streptococci, staphylococci, anthrax, bubonic plague, etc.). An insight into the mechanism of their action is furnished by treating animals with dead bacteria or with living bacteria of the same type but of low virulence, by vaccines, in other words. The resistance is specifically raised against the same bacteria and we produce by a later inoculation of the virulent type a modified disease. Instead of multiplying in many localities in the

body and killing promptly, the bacteria now multiply only in certain places, usually in lymph nodes. Here they lead to large collections of polynuclear leucocytes which form abscesses and in which still many bacteria exist. The enemy is thus held at bay and discharged outward with the accumulated dead cell masses. Only when such abscesses are internal and cannot discharge outwards is life endangered, or when accidental injuries to tissues favor other localizations. This group of bacteria also produce toxins but they are relatively feeble compared with those of the genuine toxin-producing group. This aggressive weapon is now subordinated to another, a defensive weapon, an envelope or capsule. It is this envelope that gives them power to multiply in the intimacy of the tissues. I assume that any existing toxins are aggressive, tissue-destructive, and that the capsules are protective and prevent the aggressive ferments and other anti-alien processes of the hosts from destroying the enclosed bacteria.

In the course of the host-parasite contest it is highly probable that developing antitoxins soon limit the toxic activities and that then the host must cope with the bacteria themselves. The next step on the part of the host would be a development of anti-capsular substances. Both antitoxic and anti-capsular activities prevent the bacteria from multiplying generally and they thus become restricted to the early settlement in the lymph nodes. Cultures of blood and spleen of such animals even when loaded down with abscesses usually remain sterile although the abscesses contain large numbers of bacteria. Among the invasive bacteria which produce a prolonged, usually non-fatal type of disease, multiplication occurs in one or a few localities only at the start and further inroads are associated with reduced resistance following exposure, deficient nutrition, and exhaustion. The multiplication is associated regularly with forms of protective cell reactions and cell accumulations on the part of the host. In tuberculosis the

cells form tubercles. Efforts to demonstrate definite toxic substances in the culture fluids of this type of bacteria have not been successful. It is probable that they exist only in inappreciable concentrations and that the bacillus multiplies and survives in the tubercles chiefly because of the possession of resistant envelopes or partly impermeable limiting cell membranes. The aggressive, offensive, predatory activities are, at least in part, replaced by protective devices elaborated by the bacterial cell. In tuberculosis the resistance of the bacilli is usually attributed to the fatty and waxy ingredients of the cell.

The study of immune or protective mechanisms in animals towards protozoan parasites followed the paths marked out by the same earlier studies against bacteria. Recent years have witnessed considerable activity in this field and some very interesting and suggestive data have emerged. A disease of white rats due to multiplication in the blood of a low protozoan form, the trypanosome, has been focused upon because the disease is self-limited. It affords a favorable opportunity to trace the mechanism by which the host checks the overgrowth of the parasite and sooner or later causes it to disappear. Attention has already been called to the trypanosomes which represent a very formidable group of parasites. They are responsible for the African sleeping sickness in man and for destructive diseases in horses and cattle. In a sense they have barred the way for the time being to the agricultural development of certain rich territories of the tropics. In rats the trypanosome after introduction artificially into the blood or through the bite of the flea naturally, multiplies by simple fission for a number of days, then stops and finally disappears. Taliaferro has called attention to a substance appearing in the blood during the multiplication of the parasite which checks multiplication but does not kill the parasite. This substance—ablastin—interferes with multiplication when injected into rats with the trypanosomes. The subsequent complete disap-

pearance of the latter he ascribes to a second protective or offensive substance which actually destroys the trypanosomes and which is therefore trypanocidal. We know that in spite of these inhibitory and destructive factors some trypanosomes survive, for this particular species is widespread among rats and has been a favorite object of study since Lewis first encountered it in India in 1878. This protozoan is in a kind of equilibrium with its host which ensures the continued existence of both. When we turn to the trypanosomes of the larger animals similar equilibria exist between them and certain wild species. When, however, such parasites are injected into rats or other smaller and larger alien hosts, the trypanosomes multiply until the animal succumbs. There is no early or later machinery available to check the increase.

The protozoan parasites which live within the red blood corpuscles stand in a complex relation to the host owing to the protecting intervention of the red corpuscle itself. The parasite goes through its multiplicative stage in this cell according to a timed program. It has been generally accepted that the danger period for the parasite embraced the passage of young forms to fresh cells. The checking of this process of numerical increase would automatically stop the disease, since the later sexual forms, also in red cells, are quiescent until removed by the bloodsucking insect.

Coming to the most stable parasites, those maintaining themselves in the digestive tract of the host, let us look for a moment at the roundworms. Ascaris is a nematode living in the upper small intestine. It maintains itself there for an indefinite period, the female discharging ova regularly which must pass out to continue the cycle. Bathed in the digestive ferments it withstands solution. The question has been repeatedly asked why the worm is not digested. Weinland found an anti-ferment towards both pepsin and trypsin in the

ground-up tissue of the worm; the more thorough the grinding, the more anti-ferment obtained. This was evidently very firmly incorporated with the cell substance. He was not certain whether the anti-ferment towards pepsin and trypsin are the same. Weinland's work does not locate the tissues or cell groups containing the protective enzyme. W. E. and E. L. Burge describe experiments designed to prove that if worms, roundworms as well as tapeworms, are injured or killed they are digested in activated pancreatic juice. As long as they are alive they resist digestion. According to them, the living worms resist by oxidizing the enzyme solution with which they are surrounded and destroy it. The continual oxidation and hence destruction of ferments in which the worm is bathed seems a rather wasteful procedure. Common observation shows that nature operates economically in maintaining established living organisms. It would be a severe strain on the energy output of the parasite to be continually aggressive over its entire body. Moreover the structure of the cuticle does not suggest such an active function. Perhaps there is a simpler explanation more in harmony with nature's methods. The protection of the tissues of stomach and intestines against digestion by the pepsin and pancreatic enzymes has long been a theme for speculation among biologists. The intact worm forms a part of this general problem. Northrop has shown that the living cell keeps out the digestive ferments but that the dead cell absorbs them. In other words, the dead cell becomes permeable to these destructive agents.

Returning to the highly differentiated tissues of the worm, we might offer a simpler interpretation by postulating that in the evolution of the parasitic life of the worm, the outer membrane or cuticle became entirely non-digestible, living or dead, and that it is only the ferments actually taken into the system by the mouth that come under the principle for-

mulated by Northrop. Burge states that portions of killed worms were completely digested in Mett tubes. A thin, translucent resistant cuticle left behind might escape attention. An early statement by Leon Fredericq is of interest here. He also found that *A. marginata* of the dog was acted upon only when worms were cut up. They were rapidly digested *leaving only their corneous hyaline integument behind.* Leuckart refers to the cuticula as withstanding the action of alkalies and putrefaction and remaining unchanged when the entire worm has been destroyed. Dead, collapsed worms are not infrequently found with body wall intact.

If it be true that the intestinal worms, like *Ascaris,* are protecting themselves against digestion by some continuously active process such as oxidation of the ferments which are bathing the worms, we must expect to find a greater flexibility in the parasitic relationship than is evident at present. The life of the parasite would depend on its oxidation-capacity. A slight fall in this would seal its fate. This relationship may hold for certain classes of bacteria which make good losses by active multiplication, but it can scarcely be predicated for the intestinal parasites. The theory which best fits this problem assumes that the process designed to protect the worm is carried on within the body cells which act upon the digestive fluids of the host entering through the digestive tract of the worm. The body itself is protected by a non-digestible outer covering or cuticle. The contention of Burge that the digestive ferments of the host are oxidized by the parasite remains, of course, untouched by this theory.

Under the protection of some anti-digestive mechanism then, whatever this may eventually be demonstrated to be, *Ascaris* is enabled to produce another generation in the form of immense numbers of ova which pass out of the host's body well protected by a shell. No multiplication or increase of individuals takes place in the host's body. No further mechan-

ism is needed to safeguard the parasite. It is the simplest conceivable, operating against a fairly uniform environment of digestive fluids and only upon fluids actually ingested.

In endeavoring to formulate some generally applicable theory of host-parasite relations we have seen that a number of variables enter to make the picture to be interpreted confusing. We are confronted with (*a*) Differences in host species, races, and individuals due to genetic variations and environment; (*b*) differences due to variations in parasites taking place under experimental conditions in artificial cultures; (*c*) differences due to stages of evolution and of adaptation to a partially established parasitism; and (*d*) differences due to naturally occurring or artificially produced aberrant parasitism. It is obvious that no one kind of parasitism involves all the capacities available to any one host or parasite and that an indefinite series of variations in host-parasite relationships exists. Moreover, the various anti-alien activities of both host and parasite are probably brought out by immediate reciprocal stimulation and in no generally uniform order. All we can do is to catalogue these activities in the individual and utilize them in the comparative study of types of parasitism. In general, the forces of the host may be assumed as tending in one direction, the destruction of the parasite or rendering it harmless. The parasite, on the other hand, has its mechanism set for multiplication or increase in size. The former involves processes of digestion and assimilation, the latter also. The host is not, however, dependent on the products of such digestion whereas the parasite is completely so. The host by simply checking the parasite's growth activities has protected itself sufficiently. The parasite, on the other hand, must be able to overcome the anti-alien forces of the host in at least a circumscribed territory, by destructive or neutralizing processes while increasing in numbers or developing to maturity. The parasite's ammunition consists of a variable number of

factors, such as metabolic products or toxins and such as are released by disintegration of some of the parasites, also special metabolic products of the host species which may be favorable to the multiplication and growth of parasites, enveloping protective substances, capsules of varying degrees of consistency and reproductive activities, and finally ectoplasms or limiting membranes of specific permeability or resistance to digestion. The host, on the other hand, has certain general lytic or digestive powers and the capacity to develop at varying rates antibodies which neutralize toxins and such as paralyze the growth activities of the parasite, envelop and immure it.

Any one of these functions may be sufficient on the part of any particular host to check some special parasite; on the part of any particular parasite to inhibit the host activities until multiplication has been achieved and until it has protected itself, preparatory to discharge. Thus diphtheria antitoxin is sufficient to check the diphtheria bacillus and tetanus antitoxin to protect against a future multiplication of the tetanus bacillus. On the other hand, the suppression of the tubercle bacillus may require both digestive and enveloping capacities on the part of the host.

Some significant experiments were done by Dochez and Avery in 1916 in illustrating the theme here outlined. They showed that a serum prepared in horses against the agent of pneumonia, known as the pneumococcus, strongly inhibited the multiplication of this coccus in culture fluids and caused a marked depression in its digestive powers as well as interference with fermentation processes. Serum from patients drawn during recovery from pneumonia was similarly effective. This antiblastic theory had been presented several years earlier by an Italian, Ascoli, who developed it in his studies of the anthrax bacillus. He maintained that the immune factors in the host's blood interfered with the formation of a protective capsule by the bacillus.

V

CELL PARASITISM AND PHAGOCYTOSIS

IN THE analysis of the host-parasite relationships and interactions we are quite naturally led to envisage the host cells and what goes on in and around them, what changes are observed in the course of any disturbed parasitism, for until comparatively recent years the cell has been regarded as the ultimate individualistic organism endowed with life. Today the filtrable, invisible ultramicroscopic viruses compete with it. For our present purposes we may still regard the animal cell as one of the elementary life units. Whatever happens to it is of fundamental importance. It is conceived to be the source of all active substances, such as enzymes, hormones, and protective antibodies. Though the blood itself appears on the surface to possess definite protective functions, whatever capacities it has are due to the pouring into it from all cell colonies and organs the products of their activities. The occurrence of microorganisms within the cells of higher organisms has been noted since the microscope made the cell an object of study. With the introduction of high powers and suitable staining methods, very minute objects such as bacteria and still smaller forms have been detected within host cells. The development of certain parasites after actively invading the cell, through definite stages, furnished the concept of cell parasitism. On the other hand, the presence of minute bodies such as the bacteria in cells which possess the power of ameboid motion provided the concept that the introduction was due to the aggressive activity of the cell and that it led to the eventual destruction of the ingested bacteria.

Thus we have two ideas mutually somewhat antagonistic, a more or less balanced cell parasitism and an almost purposeful destructive activity on the part of the host cell. Between these extremes we shall find numerous intergrades, for we are dealing with two variables, the character of the cell with reference to position and function in the host, and that of the parasite which ranges from a highly specialized protozoan type with a complex sexual life cycle through the smaller bacteria which multiply only asexually by simple division to the still smaller viruses. All kinds of cell capacities have been brought into play in this struggle so that every host-parasite combination may be said to differ more or less from every other.

The number of parasites introduced into a host is for certain parasites of decisive importance. We may distinguish several groups with reference to their capacity to increase their numbers within the host.

(1) Among the metazoan parasites, such as the worms, one ovum means one parasite only. (2) Among certain cell-inhabiting protozoa, one ovum means multiplication within certain limits leading to asexual descendants. These become cell parasites again in the same host. During sexual reproduction there is another definite increase in numbers. This progeny leaves the host. (3) Among the bacteria and certain other protozoa, one individual entering means an indefinite progeny conditioned on the behavior of the host tissues.

As stated above, cell parasitism may be of higher or lower degree. We may have an almost perfect symbiotic relationship at one extreme and a distinctly antagonistic relation at the other. The highest degree of cell parasitism, which is more or less symbiotic in character and apparently of no injury to the host, manifests itself chiefly among insects. Usually all hosts are parasitized and the parasite in some instances is regularly

transmitted in the egg from one generation to another. Some have been cultivated and found to be bacteria or fungi. Cowdry described symbionts in ticks specifically inhabiting the cells of the Malpighian tubules fairly large and bacillary in form, probably passing through the egg to the next generation. R. W. Glaser described and isolated in culture bacillary forms from cells in the fat body of the large American roach. Recently very minute forms have been found within the epithelial cells of the intestinal tract of insects. They bear the generic name *Rickettsia* in honor of Ricketts who died of typhus while investigating this disease and after disclosing the presence of these minute bodies in the transmitting louse. Though to all appearances harmless parasites of the insect or arachnid harboring them, they have been found formidable disease producers in man and higher animals.

A second type of cell parasitism represents a delicate balance easily upset either towards disease and even death of the host or towards resistance almost complete. Many dangerous, widely prevalent diseases of mammals, and birds come within this class or group. The parasites are protozoa with a highly complex life cycle. They are largely restricted to epithelial cells of the digestive and the renal, more rarely of the respiratory, tract. For apt illustrations we must go to animals below man, for the human race is but slightly affected and then only by aberrant forms. The use of fire in preparing foods and the choice of fruits and seeds reared above ground may have eliminated this group of parasites transmitted chiefly in the dejecta. The site chosen by such parasites permits them to escape readily from the host after a protecting resting stage has been developed. A formidable group is represented by certain sporozoa, called coccidia, which live during their entire life-cycle in epithelial cells of the digestive tract of mammals, birds, and lower forms. Very rarely man

has been found infected. Each animal species has its own variety of coccidia. In some countries or localities they produce fatal epidemics, especially among cattle, poultry and game birds. The life-cycle is briefly as follows: The motile spore products penetrate certain cells of the host and following an expansive growth within the cell break up into a number of mobile asexual merozoites. These having destroyed the original host cell in turn enter fresh cells and go through the same cycle, thus multiplying by repeated asexual generations. They stop after a time and the vegetative merozoites entering fresh cells develop into male and female gametes. The resulting sexual product or ovum goes on breaking up into a definite number of sporozoites within a protective shell. This passes out and on entering a new host the shell is digested away, usually in the duodenum, and the escaping sporozoites start a new cycle by entering epithelial cells. Not only the digestive tract but also other tracts which are in open communication with the exterior may harbor coccidia. The renal epithelium provides a convenient abiding place. The sporozoites or sexual products penetrate the mucous membrane of the digestive tract and are carried by the blood stream to the kidneys where they settle down in cells of the convoluted tubules or the collecting tubules and even in the epithelial cells of Bowman's capsule. Conjugation takes place and the product is discharged in the urine.

In this type of parasitism the host cell is probably destroyed but numerous mitotic figures in the epithelium indicate that up to a certain point the losses are replaced. Only when the invading individual sporozoites are very numerous is the host's life in danger because the stripped mucous membrane then becomes permeable to bacteria. The more or less unerring orientation of these parasites towards the particular cell group in which they find lodgment is, to be sure, matched by

activities in other forms of life, but it is always imposing when we come face to face with it.

Among this group of cell parasites there exist species which, so far as we know, are in equilibrium with their hosts and do not affect the host's well-being appreciably. Just how the balance is maintained is not clear. The inhibition must be focused on the non-sexual stage of multiplication. When this is reduced to a minimum compatible with the continued life of the parasite as a species, the relation approaches a harmless parasitism. Evidence indicates that in such relationships all host individuals go through the process of being parasitized early, with birds, for example, in the nest. The parent birds are the carriers.

Another large, highly important group of parasites have selected the red blood corpuscles of some vertebrate host in which to pass a portion of their life-cycle and to multiply asexually. The cycle is completed by some blood-sucking insect or arachnid which draws the parasite in the red cells out of the blood of the vertebrate host. In the insect sexual reproduction goes on and leads through a certain limited multiplication to spore inclusions, called sporozoites. These have a certain degree of mobility which enables them to move forward into the mouthparts of the insect or arachnid. When the latter bites another host, it injects the new individuals into the blood where the same process of parasitizing the red corpuscles and multiplication in them is repeated. In man, malaria in its several forms is a conspicuous example of red-cell parasitism. In domestic animals, among them cattle, horses, and sheep, several other parasites of the red cell are equally destructive.

In these diseases a certain equilibrium is eventually established probably through natural selection. The disease then begins at an early stage and the survivors are relatively im-

mune but still harboring parasites. How this comes about remains to be determined. The relative fragility or resistance of the red blood corpuscles to invasion may be one factor to determine the outcome. If these cells in any individual should manifest a certain premature fragility after entry of the malaria or other blood parasite, the latter would be unable to multiply and the disease cut short by what may be called hypersusceptibility. On the other hand, certain cells might oppose entry through some specially resistant condition of the cell wall. Immunity would then be due to a hyposusceptibility. Changes in the host species would conceivably move from the hypersusceptible through the normally susceptible to the resistant. The resistance of the adult in malarial regions may be due either to changes in the red blood corpuscle or to humoral antibodies acting on the free stage before entry. Sachs has stated that the blood corpuscles of freshly hatched chicks are not sensitive to the poison of the garden spider. On the other hand, they are susceptible to the action of cobra toxin which fails to act on those of the adult. Though the red cell is no longer a cell in the sense that it possesses a nucleus and is capable of division, any change in it may be due to the influence of substances from the parasites acting on the bone marrow where the red cell is in process of development. The animal body has a remarkable capacity for replacing red cells, yet the parasitic invasion of these cells by successive non-sexual generations of the parasites may be so great that the number in the circulation is reduced to from one-half to one-fourth of the normal. The breaking up of red cells may seriously clog the liver and the foreign protein of the parasite may cause protein intoxication.

Not only epithelial cells of variously located mucous membranes and red blood corpuscles, but also striated muscles cells are the sites of protozoan parasites. These are known as

sarcosporidia and occur in nearly all domesticated animals. The life-cycle of the parasite is unknown, except for the form found in the house mouse which is transferred to other mice when they gnaw the carcass of some infected dead mouse. The parasite appears as a minute body in the center of a muscle fiber where it develops a large, presumably asexual generation. Some remain microscopic in size. The species in the mouse becomes as long as the muscle fiber and conspicuous to the naked eye. Even metazoan parasites may parasitize cells. *Trichinella spiralis,* the dangerous swine nematode which caused so much disease and many deaths in the nineteenth century and is still not fully under control, lives in its larval stage in the striated muscle fibers of mammals and is readily conveyed to man when infested raw pork is eaten. The coiled worm, resting in the muscle fiber, when ingested by some mammal or man rapidly develops to maturity in the intestine. Large numbers of living young are born and set free there. They penetrate the mucous membrane and are carried by the blood stream to all parts of the body. In the capillaries they bore their way out and into muscle fibers, coil themselves up, secrete a protective capsule around themselves, and remain alive awaiting ingestion by another host for as long as twenty years.

We have now viewed a number of relations in which the parasite occupies a cell of the host. These relations range from complete accord to violent disturbances, due to quantitative destruction of important cells. The conflict appears chiefly as mechanical destruction associated with physiological disturbance on account of the amount of cell débris both native and foreign to be worked over by the host. No aggressive activities on the part of the host appear on the surface in this conflict but in the long run a specific immunity of exposed populations does appear.

There is another group of host-parasite cell relations in which the conflict is more in evidence. The cells involved belong to certain groups endowed with ameboid mobility and migration tendencies or capable of entering into these states under appropriate stimulation. They embrace the white cells of the blood and certain tissue cells, all descended from the mesenchyme. Certain ones, like the polynuclear cells of the blood, are normally reproduced in the bone marrow and the lymphocytes in the lymph nodes. Certain others arise in the connective tissues. Recently this latter group of tissue cells has been denominated by Aschoff the reticulo-endothelial system. The cells of this system occur in the spleen, lymph nodes, and in connective tissue in general. They may be regarded as sessile in distinction from those which appear regularly in the blood in fairly definite numbers. One or the other of these cell groups becomes conspicuous in any infectious disease. Each diseased condition manifests a type of cell behavior or reaction which may be qualitatively or quantitatively distinguishable, and which is again modified according to the host species involved. Ostensibly these cell groups have normally no definite functions such as are performed by the highly specialized cells of the central nervous system, the liver, kidneys, intestinal tract, and pancreas. They represent a universal matrix. It is a commonly accepted theory that their chief function is protection and we might compare some of them to police and others to reserve troops to be called out in certain emergencies. It had been noticed by Koch that some pathogenic bacteria are always found within cells. He also noticed that tubercle bacilli are within cells. In 1884 Metschnikoff first emphasized the importance of some of these cell groups in taking in bacteria and formulated his theory of phagocytosis as the chief factor in destroying alien organisms. The botanist Pfeffer had already pointed out that cells of

this type are attracted by certain substances in solution. Not content with pointing out the relation of phagocytes to infectious processes, Metschnikoff brought together a variety of activities going on in the normal organism which he associated with phagocytosis. Thus, the metamorphosis of insects, the absorption of the tadpole's tail were referred by him to the action of phagocytes. In pathological processes, the muscle cell invaded by trichina larvae becomes, according to him, for the time being, a phagocyte. The resorption of extravasated blood, of the exudation in pneumonia, the disintegration and removal of dead tissue, the disposition of foreign bodies, of dust and pigment, were pointed out as preeminently the task of certain phagocytic cells. If the body controls this machinery as scavenger to get rid of unnecessary and obstructing material it is but a step to invoke the same mechanism in the disposal of living foreign organisms. It is unnecessary here to call attention to the controversies raised by Metschnikoff's work. They are now largely history. It is common observation that particles foreign to the organism sooner or later are found within the normal or swollen cytoplasm of certain cells. A discussion of the different views held by histologists and pathologists concerning the derivation of some of these cell groups known as monocytes and clasmatocytes is foreign to my subject. These views quite naturally depend on the material, experimental or comparative, which the different investigators have had before them. Thus Maximow regards monocytes and clasmatocytes as related and as developing under special conditions from lymphocytes. Sabin and associates distinguish between these cell types with the aid of neutral red. This dye forms rosettes of stained vacuoles in surviving cells of the monocyte group but not in clasmatocytes. A satisfactory formulation of the activities of the different mobile cell groups will require the special study of many

disturbed conditions in which they come into play. Only after this has been done will a comparative study be possible and an underlying common theory attainable. Thus in certain acute diseases, the polymorphonuclear cells appear in increased numbers in the blood stream or in certain organs where they form abscesses. In more chronic types of disease the lymphocytes form colonies in various organs and tissues. In the presence of the larger parasites the eosinophile cells flood the region about the parasite. In still other, more slowly developing, diseases the monocyte dominates the invaded territory. The various assemblings, gatherings, invasions are the result of responses to certain specific stimuli from injured tissues and from the parasites, and they give the disturbance its peculiar characters.

Normal phagocytosis, as stated above, is a phenomenon associated with the physiological processes of removing and preparing certain waste products for discharge or restoration to renewed use by the system. The destruction of worn-out red corpuscles or those injured in diseased regions of the body is largely undertaken by certain cells of the spleen. Following the injurious action of certain diseases the spleen contains many cells filled with weakened red corpuscles. Often one may see a dozen or more red corpuscles in a single phagocytic cell. They slowly disintegrate and melt together into irregular orange pigment masses. In the liver certain cells lining the capillaries carry on similar functions. In the air cells of the lungs certain cells pick up inhaled soot and mineral particles. In certain diseases, some of the bacteria responsible are regularly found within phagocytic cells; in others, only under certain conditions which imply either an acquired resistance of the host invaded or a lowered virulence of the invader. In the early days of bacteriology all phagocytosis was regarded by one school as the first stage of a process of

intracellular destruction which inevitably followed ingestion of bacteria. Another school maintained that the injury to bacteria took place in the blood or lymph and that the subsequent ingestion of bacteria was merely a process of removing dead bacteria or at least completing the destruction. The question gravitates around the problem to what extent the cell is successful. Data thus far in hand indicate that each disease and each microorganism must be investigated to determine this outcome. In the cell parasitism of protozoa already discussed the parasite enters the host cells actively in a motile stage. In the few illustrative diseases due to bacteria, to be described, the host cell is the active agent. There is no evidence at hand that shows active penetration into cells by bacteria. Moreover, nearly all the bacteria found in phagocytic cells are non-motile.

The most conspicuous illustration of bacteria in cells was described by Koch. He produced a disease in mice by injecting subcutaneously a little water from a surface drain. In this fluid a minute bacillus happened to be present which caused a rapidly fatal disease. Later it was found that the bacillus is the cause of a widespread disease of pigs which Pasteur studied for a time with the object of developing a vaccine. In the mouse and the pigeon, which is also highly susceptible, the bacilli are found within endothelial cells of capillaries. Whether the bacteria are in part at least destroyed within these cells is not known. In spite of the manifest phagocytosis, the disease in mice is always fatal; in pigeons, phagocytosis is equally powerless as a protective mechanism. Mouse septicemia is an acute disease and fatal in three or four days. The other diseases to be mentioned as illustrating phagocytosis are chronic diseases, beginning insidiously and lasting months and years. Tuberculosis is one of these. The beginnings of this disease are due to the deposit of perhaps a single bacillus in a

lymph node whither it was carried in the lymph stream from some air vesicle of the lungs. Here the bacillus multiplies and the progeny is soon enveloped in cells which belong to the lymph node structure and which may also increase in number under the stimulus of the tubercle bacillus. As the tubercle develops in a centrifugal direction there comes a time when the central portion of the cell mass dies and a partial capsule is formed around the whole. The process is thus completed for a time at least. If something occurs to open or partly disintegrate the tubercle, the enclosed surviving bacilli are carried to other territories in lymph or blood stream and a crop of secondary tubercles is formed. In the early stages of the disease, there appears a change in the entire host owing to the presence of the tubercle bacilli. This change was first noticed by Koch. The body now reacts differently towards newly introduced bacilli. Its behavior is speeded up and the bacilli are more promptly fixed and brought to a standstill. This changed attitude is known as allergy. It is associated with a newly acquired susceptibility to a soluble product of bacterial growth known as tuberculin. When injected under the skin it produces a fever in the tuberculous. When injected into the skin a local reddening with swelling appears not recognized in the non-tuberculous.

Much has been written in attempts to elucidate what goes on in the tubercle and the relation of the local to the general hypersensitive or allergic reaction. Just how the tubercle bacillus acts before and after the tubercle has been formed has not been cleared up. That bacilli are destroyed in the cell complex formed into the tubercle seems fairly certain. It is also definitely known that bacilli survive for long periods in the central dead nucleus of the tubercle. The relation between bacilli originally produced and those surviving is an unknown quantity. Evidently a complex interrelationship, a

play back and forth has been evolved which both protects the host from inundation by bacilli and some of the latter from destruction by segregation in the dead tissues and by the surrounding fibrous capsule. Another disease due to bacilli very closely related to tubercle bacilli is known as paratuberculosis. It gives us a very good perspective of our ignorance of the intimate constitution and capacities of these minute organisms that cause tuberculosis and paratuberculosis. The latter disease, thus far known only to affect cattle, involves the mucous membrane of the intestines in which the bacilli may be present in enormous numbers. All bacilli are within cells of the host which are stimulated to expand in size by the presence of the bacilli. In general the disease leads to the death of the cow in spite of the fact that all bacilli are interned in host cells. Many interesting points of similarity and unlikeness might be pointed out between these two diseases, the microorganisms of which are so nearly indistinguishable. In the diseases mentioned, to which we may add leprosy, the conspicuous phenomenon is the presence of cells not normal to the body but obviously derived from existing cells such as those lining lymph spaces and channels. Under the influence of the alien bacilli the cells swell and surround and enclose the bacilli in contact with them, or the swelling may take place because of certain metabolic products or enzymes of the parasite, effective at a distance. The inclusion may thus not be an active reaction on the part of the cell, but a combination of passive and active processes in which the relative dominance of one or the other process may decide whether the local disease is to go on or to be checked.

In the more acute parasitic diseases certain other cell groups dominate the field. Polymorphonuclear cells, the white cells of the blood, developing in the bone marrow and always present in the blood stream in definite numbers normally, be-

come more numerous and active. Some meningococci, gonococci, staphylococci, and streptococci are always found within these cells during the diseases caused by them; and it is generally assumed that the more active this phagocytosis, the greater the protective reaction of the host. In our experiments with animals and animal diseases, this form of phagocytosis is regarded as a definite sign of a lower virulence or a greater host resistance. The inference of medical science, judging always from the side of the host, is that if this process can be artificially activated or increased above the level found in disease, the host or patient would be benefited. Numerous researches have been carried on to account for the increase in phagocytic activity of polymorph cells. Denys of Louvain first showed by experiments that if leucocytes, streptococci and normal rabbit serum be mixed in a test tube no change is observed. If, however, leucocytes and streptococci and serum from a rabbit which had been repeatedly treated with injections of dead streptococci be mixed, the cells would begin to ingest the streptococci. This experiment thus introduced a humoral or blood factor which is developed during disease or artificial immunization. It is known as bacteriotropin. About the same time it was shown by Almroth Wright that there exists in the blood of individuals normally a substance having the same but less pronounced stimulating effect. This substance he called opsonin. Experiments clearly demonstrated that the bacteria become coated with the opsonin or tropin and in this condition become acceptable to the leucocytes.

In the processes involving the abnormal, epithelioid cells of tuberculosis and paratuberculosis the leucocytes play no active part. The presence of humoral or blood factors is not recognizable but they may be developed later as an outcome of the local process insofar as substances may be set free into the

circulation from the tubercle and epithelioid tissue. In tuberculosis the entire body becomes allergic and secondary tubercles remain small. In paratuberculosis the allergic state does not dominate the scene, if indeed it appears at all. This and other data indicate a higher parasitic level of the paratubercle bacillus—relative absence of offensive weapons and a marked development of protective capacity.

The source of opsonins and tropins according to current theories is cellular. Just what group or groups of cells join in producing these substances is under discussion. At present the tendency is to look at the reticulo-endothelial system as the source of antibodies. No general inclusive theory can be formulated since every host-parasite relation is built up by factors differing much or little from other relations. It is fairly certain that bacterial substances (so-called antigens) circulate widely in the invaded host and that a variety of cell groups may be stimulated by them, some earlier, some later, in furnishing the protective antibodies. The active circulation of the higher warm-blooded animals becomes the important vehicle in distributing the protective antibodies of the host discharged from the stimulated cells to all parts of the system.

It was Metschnikoff's great service to have pointed out the antagonistic relation between bacteria and cells containing them. He acknowledged that bacteria may perish within them or overcome the cells. Enthusiastic followers have not sufficiently recognized the limitations he himself accepted. Their interpretation of phagocytosis as definitely destructive towards the inclusions was subjected to a heavy strain when antitoxins were discovered. In fact the humoral factors in effecting a resistant state dominated theories of immunity for a time and thereafter phagocytosis was regarded as a process the outcome of which could not be predicted. In 1916, Rous and Jones demonstrated the occasional protective action of

phagocytosis toward ingested bodies. They showed that when typhoid bacilli are ingested by leucocytes in the test tube, they are protected against a bactericidal serum. Within such cells, the same bacteria are shielded from the destructive action of potassium cyanide. Likewise red cells taken in by phagocytes are protected against a serum which would lake them.

The distinction between mobile parasites entering immobile cells and non-motile bacteria taken up by mobile cells is not sharp, for there are protozoa which multiply in phagocytic macrophages and bacteria in passive epithelium. In a disease of cows, limited to the fetal membranes in pregnancy and resulting in the premature discharge of the fetus, the bacteria responsible for the disease are very minute. The disease starts in a filling up of the epithelial cells covering the outer fetal membrane or chorion with these minute bacteria and acts like a surface or prairie fire in destroying these covering cells and sooner or later obstructing the fetal circulation. This bacterium, under certain conditions not definitely known, may cause one variety of undulant fever in man when it is ingested in milk or is brought in contact with fresh wounds of the integument. In a tropical disease—kala-azar—in which a minute flagellate is the pathogenic factor, the flagellate appears as a roundish, non-flagellate body within reticulo-endothelial cells of liver, spleen, and bone marrow. The parasites apparently do not suffer from their confinement in what is regarded as host-protective tissue.

Attention has already been called to a group of pathogenic organisms, the *Rickettsia,* much smaller than bacteria but still visible with the highest powers of the microscope, as the cause of formidable diseases, among them typhus fever and Rocky Mountain spotted fever. A fatal disease of sheep in South Africa, called heartwater, is due to a member of this genus. They are mentioned here because they are taken in by

the lining cells of the minute blood vessels, the vascular endothelium. The *Rickettsia* are most likely of insect or arachnid origin. Typhus is transmitted by lice, Rocky Mountain fever and heartwater by ticks. Organisms similar to the pathogenic *Rickettsia* but not disease-producing are also found in insects. The evidence points to some parasitic adaptation of these forms to temporary life and multiplication in the vascular endothelium of man and higher animals, whence they are again recaptured in the blood withdrawn by insects. The *Rickettsia* forms of Rocky Mountain spotted fever are hereditary in the tick; that is to say, they pass from the adult female into the ova and thence into the developing young. It is thus not necessary for the continuance of the microbe to pass through a larger host to complete its cycle. On the other hand, the microbes of typhus and heartwater require the larger host to complete the cycle. There would then be both infected and non-infected intermediate hosts in nature. The capacity of these minute forms to find lodgment and multiply in vascular endothelium makes them a dangerous group. Mortality is high. The distinction between fatal and non-fatal cases may rest in the amount of infectious material introduced by the louse or tick or the varying virulence of the microbe itself. In endemic regions the inhabitants may also possess some immunity acquired by attacks or through natural selection. The struggle is probably decided in the endothelial cell.

The importance of evaluating accurately the significance of humoral and cellular functions in suppressing parasites is evident when the possibility of a protective or curative agent in blood serum of treated animals is under consideration. In general the relation between humeral and cellular activities are as follows: When the defensive weapons of the microorganism coincide with its offensive activities and are dis-

charged into the blood stream, the host activities are absorbed or directed in producing antibodies which when enough of these are on hand will win the day. The host defenses then are general, humoral. When the offensive weapons become defensive in that they are more closely bound to the parasite as in the form of capsular material, the antibodies produced against this, when adequate, neutralize or dissolve it and bring the stripped microbe within the destructive action of the normal body defenses. It is then dissolved or taken into phagocytic cells to be more gradually disintegrated. The process is then both general and local. Finally, when the defenses of the microbe become more closely identified with the structure of the organism itself, reducing permeability to a minimum, then the ingestion by special cells is followed by a long-drawn contest within the host cell. The process is then almost wholly local and cellular. It is this latter phase in which serum therapy can do little or nothing, and it is the existence of this phase in tuberculosis and like diseases which makes a complete serological cure impossible. It must not be forgotten, however, that if immune sera can take care of all the toxins, etc., which enter the blood stream, the protection afforded may localize and shut in the disease process.

The determination of both the bactericidal action of the blood and the destructive action of bacteria interned in host cells is complicated by the absence of any very precise signs of death in the bacteria. The one upon which reliance is placed and one used universally in testing the lowest thermal death point of bacteria in milk, in foods generally, in testing the performance of filtration and sewage plants and the efficiency of disinfectants, is the capacity to multiply when the material containing the bacteria is transferred to some growth-favoring medium or substrate. For all practical purposes, absence of signs of multiplication is an adequate indi-

cation of death. It is not, however, infallible, since bacteria which appear dead in one culture medium may multiply in another. The quality of the available food may revive an injured bacterium. The reducing action of dyes, especially methylene blue, has been used in determining the viability of leucocytes. This action is of little use in bacteriology since bacteria killed by heat may reduce this dye in the absence of oxygen. For pathogenic bacteria the production of disease in inoculated animals is a satisfactory indication that the injected bacteria were alive. It may, however, fail when the surviving bacteria injected are too few in number. Signs of disintegration of bacteria are now and then observed but even they may be misleading. Fragments regarded by some as signs of death have been considered living forms of a definite growth cycle by others. All form changes among bacteria have had various interpretations given them since any demonstrative convincing proof of any one interpretation is lacking.

It is not to be supposed that inquiry into the host-parasite complex would stop at the general interpretation here offered of aggressive and protective functions, for they simply represent a general attitude of living things as contrasted with their products. The introduction of physico-chemical analysis into all the phenomena exhibited by host and parasite has already made much progress. The use of ultraviolet light, of x-ray, radium and direct sunlight is showing results in producing pathological and genetic modifications, the main service of which is in interpretation. The capsules of bacteria have been analyzed, the various antigen-antibody reactions are being referred to surface phenomena and electric charges investigated. Mudd has shown that the tubercle bacillus in an aqueous phase in contact with an immiscible lipoid phase will be drawn into the latter. The bacillus is thus shown to have lipoid in its outer zone. When the bacillus is exposed to

and coated with a specifically immune horse serum the entry of the bacilli into the lipoid phase is halted. A normal serum fails to act in this way.

There remains the problem of specificity of action of the antibodies. Why the injection of certain substances, called antigens, should call forth in the animal body so many different highly specific antibodies which can be demonstrated in the blood or serum, has thus far baffled interpretation along physico-chemical paths. The solution, when it comes, may appear relatively simple. Ehrlich suggested an explanation, known as his side-chain theory. He postulated that the protein molecule in the cell was made up of a central nucleus and numerous side-chains. The injection of a given substance stimulated one of these into activity. With increasing prolonged stimulation these side-chains became overproduced and discharged into the blood as antitoxins or other antibodies. The theory demands an unlimited number of side-chains to account for the hundreds of antibodies produced experimentally since the original discovery of antitoxin. Though derided in recent years the hypothesis has been highly stimulating and suggestive and still awaits something to take its place. As long as life is not reduced to a formula, those who study living things are compelled to assume something more in their behalf than what is offered at present by physico-chemical research.

In summing up the theory of the host-parasite conflict as built up in these pages, the writer assumes that the so-called offensive or aggressive weapons of the host belong to his normal physiological activities and that they are in general lytic or dissolving. Similarly those of the parasite are brought from the free-living ancestral state and are essentially toxic, lytic, or destructive. Those activities called self-protective in both host and parasite may be regarded as developed in the

evolution of parasitism and adjusted finally to bring about the particular host-parasite equilibrium. Stated in another way, in the evolution of parasitism, there has been shoved in or interposed between the general anti-alien activities of the host and the vulnerable evolving parasite a new substance (capsule) or a new state of the surface of the parasite. This demanded an overdevelopment of a special mechanism on the part of the host in the formation of specific antibodies and in the adaptation of certain normally phagocytic cell groups to the internment and gradual destruction of the parasite.

VI

VARIATION AND MUTATION AMONG PARASITES

IN ATTEMPTING to penetrate the mysteries of epidemics, their rise and decline, and the appearance of new diseases, science is confronted with several problems, among them the variability of the host and that of the parasite. Either one or the other, or both, must vary, to account for the rise and fall of infectious diseases. During the period preceding the introduction of the methods of Koch for the isolation and cultivation of bacteria and fungi on solid substrates the imagination of scientists and pseudo-scientists was active in picturing the transformation of one species of microorganism into another. This tendency was promptly checked by Koch and his associates. It may be that his somewhat rigid adherence to the doctrine of the fixity of the characters of bacteria and his indifference to studies which pointed to tendencies among definite species of bacteria to form varieties was a reaction against the wild extravagance among certain investigators of his day and the slovenliness in methods of cultivation which readily served as a means for apparently producing transformations of definitely characterized types into one another. Today the attitude of microbiological science tends to mediate between somewhat extreme positions and recognizes a certain plasticity within limits not easily defined, which plasticity does not in any way threaten the superstructure of medical and sanitary science built on the constancy of pathogenic species. The work of the past generation has revealed a fundamental stability of the characters of microorganisms with restricted variability. This position has

not been won without struggles, but it would be out of place here to more than allude to the controversies which have been carried on over the specificity of almost every important pathogenic microorganism whose identification gives us little or no trouble today. From the very beginnings then of the study of pure cultures of bacteria and protozoa, there have been noticed variants or races of organisms which cause major diseases in man and animals. The intimate genetic relation of the races could not be denied, yet the developing methods of study brought out certain tenaciously maintained, chiefly physiological differences.

There is scarcely a specific disease known today whose causal organism is not represented by at least several variants, or a parasite which does not appear under several forms. We may call them variants, races, or even species. The results of investigation have been quite invariably the same. Some one discovered a microorganism responsible for a given disease. Later discoveries brought to light the same factor but with certain characters which distinguished it from the one first discovered, and so on to other variants. The subjective factor or the personal equation naturally plays a certain part in recognizing relationships or in associating forms at first regarded as unrelated. All classifications and groupings are man-made and require for their acceptance a certain unanimity or agreement. It would be transgressing the limitations of this study to catalogue all the interesting variants discovered one by one. Such a catalogue might well fill a volume and develop into a special history of microbiology during the past half-century. Certain illustrations are, however, necessary to drive home the significance of this factor of variation as a powerful weapon in the hands of nature.

The most readily distinguished races of the same parasite are those living on different host species. The tubercle bacillus

parasitizes man, cattle, and poultry. The form of the bacillus and the kind of tissue it tends to stimulate are much the same in these hosts. The races were not separated by the discoverer. Only after considerable analytic study by others were certain definitely distinguishing characters brought to light. Though the bovine race or type of tubercle bacillus may produce certain forms of tuberculosis in man, chiefly in the young, nevertheless it is readily distinguishable from the type which invades man. On the other hand, the one associated with man does not attack cattle. The avian race of tubercle bacillus is restricted in its devastations to poultry although it now and then produces local disturbances in other animals. Prolonged attempts to change types have thus far failed. The bacillus of so-called undulant fever in man is known under several recognizable races which have an essentially animal habitat. There is the bovine race, producing a disease in cattle leading to premature expulsion of the fetus which has caused heavy losses wherever dairy cattle are kept. There is the disease in swine associated with a distinct variety of the bacillus, and lastly the goat and sheep variety causing much human illness in Mediterranean countries as a result of contact with these animals and the use of goat's and sheep's milk. Even the horse is at times attacked and extensive local suppuration results. These types or races are genetically related and they differ but slightly from one another. They are not infrequently found in alien hosts. It is this aberrancy which leads to undulant fever in man.

Among the more common everyday forms of pathogenic bacteria, the septic or pus bacteria, known as streptococci and staphylococci, exist in a variety of racial forms which parasitize man and domestic animals. Their aberrancy or migratory tendencies have not yet been studied exhaustively and it cannot be definitely stated how far animal forms infect man. It

is known, however, that human streptococci, among them the form associated with scarlet fever, occasionally reach the cow's udder where they multiply in the milk ducts and at each milking are taken out in large numbers. Severe epidemics of septic sore throat with at times a high mortality have been observed for many years and now, owing to the improved bacteriological technique, they can be traced to the individual cow. In this relationship the cow's udder acts as the involuntary culture tube for a human disease germ.

A group of animal diseases, known as paratyphoid fever because of their resemblance to typhoid fever of man, is characterized by a number of variants distinguishable chiefly, if not exclusively, by certain host reactions. They are closely related to the typhoid bacillus. Among themselves only serological tests, such as the agglutination test, bring out differences. The tendency of paratyphoid bacilli to multiply in the human intestine as a result of eating inadequately cooked food, especially meat, and to set up a prolonged fever made vaccination against this disease a routine practice during and after the World War.

There are various pox diseases appearing in man, sheep, swine, horses, and poultry which have many characters in common that point to a common ancestry. In the cow, the disease is known as vaccinia. It causes eruptions on the udder which provide the material for the vaccination of human beings. It is now generally accepted that cowpox is smallpox greatly modified and mitigated in the cow, although it is not definitely excluded that it may not have been derived from horsepox. The host limitations of the different races of pox virus are still to be determined.

Among the protozoa the flagellates known as trypanosomes, discussed in an earlier chapter, have characteristics more like the bacteria than any other protozoa. They multiply

freely in the blood like septic bacteria. They produce disease in a variety of hosts and they are intimately involved in the fate of human civilization in the tropics. One race, *T. brucei,* attacks cattle. Three other races produce an equal number of diseases in horses. Two are responsible for the African sleeping sickness in man. Each produces disease when injected into a variety of animal hosts other than the one in which it occurs in nature. There is still much uncertainty concerning the source of the human disease. Some regard it as the result of infection coming from animals through biting flies and have suggested the destruction of all wild beasts in the sleeping sickness areas. Others are equally positive that animal sources are of little significance compared with infected man and strongly advise against the destruction of animal life. Another flagellate, Leishmania, which figures as a pathogenic agent in the tropics in human beings and in dogs is separable into two races, one producing external lesions, the so-called Aleppo boil, and the other internal lesions, most conspicuous in the spleen.

Among the sporozoa similar problems confront the biologist. Tyzzer has described four species of coccidia invading the epithelium of the intestinal tract in chickens. These had been regarded as one hitherto. Since the complex life cycles of these parasites are more or less alike it is not surprising that they should successfully parasitize the same host species. Among the ciliates *Balantidium coli* of the domestic pig may or may not prove to be identical with the *Balantidium* found in certain cases of intestinal disease of man. Among the higher intestinal parasites there is a close relationship between the lumbricoid worm, *Ascaris,* in man and swine. A distinction between the two narrows down to the question whether the *Ascaris* of one species can live and reproduce in the intestine of the other—a proof difficult to carry through experi-

mentally. The whipworm, which is found in man, cattle, swine, and dogs, may or may not represent four distinct races. Among ectoparasites the various mites known as *Sarcoptes,* which attack man, horses, sheep, dogs, cats, and pigs, and *Demodex,* which is found in dogs, pigs, cattle, and man, are so closely related as to suggest a common ancestry in the distant past.

If we maintain that the host tends to modify the parasite enough so that the invasion of different hosts by the latter necessarily leads to races, we are also faced by the fact that different races of the same parasite may be found in the same host. How can we account for these modified forms in the same host? Thus among the bacteria there occur races differing in virulence and races which are distinct with regard to their antigenic qualities. This means that protective sera prepared in horses, for instance, against one race may be inactive against others. Diphtheria bacilli differ markedly among themselves in the capacity to produce toxins. Fortunately the antitoxin prepared with one strain is effective towards others. Differences exist among influenza bacilli, meningococci, streptococci, and staphylococci. To overcome the inefficiency of monovalent protective sera, horses are treated with a mixture of races of bacteria to ensure a wide protective action of the resulting so-called polyvalent sera. There may be cited several factors cooperating in maintaining races of divergent characters in the same host species. The localization in different tissues may contribute. There may be in certain species of unicellular parasites a converging evolution through which distinctive characters are lost or reduced below recognizable values and which tend to make the species closely resemble one another. The different grades of virulence are more easily explained since virulence is a quantitative, variable character readily influenced by certain manipulations. Certain variable

conditions of food, soil, and temperature depending on geographical factors may influence the host sufficiently so that races of parasites may arise which differ in certain features from those in another continent or climate.

Bacteriological technique has made minor differences among bacteria readily recognizable. In the study of those agents of disease which so far have been invisible with the aid of the modern microscope there are, however, not available any such methods. Only through their effects on animals can they, as well as differences among any group, be recognized. Recently some of these viruses have been made to multiply in a mixture of animal tissues and fluids. This represents a definite step in advance. These ultramicroscopic viruses have in certain instances been distinguished with the aid of serological tests. Thus the sera from two animals treated with two strains of virus might be reciprocally non-protective, which interpreted according to currently accepted standards would mean two distinct races of the virus. The virus of poliomyelitis has been shown to differ somewhat in different epidemics. The virus of rabies appears under at least two races and it is probable that the distemper virus of dogs may not prove to be homogeneous. Such differentiations must not be confounded with degrees of virulence which stand for mere quantitative differences.

According to Löffler and Frosch, the first to demonstrate the existence of ultravisible viruses in animals, the virus of foot-and-mouth disease if transmitted artificially within the same susceptible species, cattle or swine, loses its virulence after three or four passages. This is, however, maintained if the virus is transmitted from cattle to swine and back to cattle in a zigzag series. Since the fundamental studies of this virus, later investigators have shown that actually three varieties of this virus exist. They can only be distinguished by allowing

the specific antibodies of each, developed in the inoculated guinea pig, to act on the others. Neutralization of the capacity to produce disease when one virus is mixed with immune serum produced by virus from another source is the sign of identity. It is of interest to point out here that the three viruses may have been developed on the three different hosts of this disease. An interesting illustration of varieties among diseases is furnished by one known as alastrim or milkpox which occurs in South Africa and Brazil. It has certain undeniable points of relationship with our smallpox. It differs from the latter in low mortality, absence of secondary fever, and early formation of pustules. The period of incubation is the same as for smallpox and the vaccine for the latter protects against milkpox.

The discovery of races and varieties in nature has been matched in the past fifty years by the activity of the laboratory in attempts to produce new varieties. These attempts were begun and greatly stimulated by the pioneer labors of Pasteur. Since much that has been done has been focused on the problem of virulence this concept requires some analysis. When we refer to a parasite as pathogenic we mean that it is capable of producing some disturbance of the physiological equilibrium of the host. The degree of disturbance involves a higher or lower virulence on the part of the parasite's activities. Virulence may also mean the relative capacity to enter and multiply in a given host. A streptococcus which infects by being placed merely on a shaven surface of the skin is more virulent than one which must be deposited in or under the skin with a hypodermic needle. In general virulence signifies capacity to multiply rapidly in a given host in contradistinction to the capacity to multiply less rapidly but to persist more tenaciously. The concept thus varies with the parasites since the type of multiplication and response will be different.

The artificial cultivation of bacteria and certain protozoa has been of incalculable benefit in the analysis of disease processes. It gave into the hands of the pathologist living things quite independent of other unknown factors even though the living things themselves were very complex and only superficially known. However complex their structure and function they acted as units in experimental research. Two major objectives can be discerned influencing this field of work: first, to maintain intact the characters of the cultivated organisms; and second, to modify them in certain directions, especially towards a lower virulence.

The development of culture methods has been rather empirical. The earliest fluid medium, hay infusion, gave way to bouillon, which still forms the basis of much culture work. The source of pathogenic bacteria being animal tissues, the next step was to use bits of tissue and blood as additions. More complex media were devised as the difficulty of culturing certain bacteria was recognized. Koch used coagulated serum for tubercle bacilli, which was later replaced by media containing egg white and egg yolk. One species of bacteria has been stimulated into growth only by incorporating heat-killed closely related bacteria into the egg medium. Certain bacteria, notably the pneumococci, have been comprehensively studied with reference to favorable media and two substances found to be cooperatively necessary, both being present in blood. One of these is killed at 120° C., the other not. One is replaceable by such vegetables as tomato, pea, and bean extracts, and by yeast. Certain bacteria fail to multiply in the presence of oxygen. These are known as anaerobic bacteria. Certain bacteria, like *Brucella abortus* from cattle, multiply in the earliest cultures only in the presence of CO_2 and their growth can be suppressed by simply placing a small vial containing sodium or potassium hydroxid in the mouth of the culture tube which

is then sealed. Some bacteria gain something from the growth of certain other species on the same solid substrate. Influenza bacilli are greatly stimulated by the neighboring colonies of certain other bacteria and form a kind of "satellite" growth. It should also be mentioned that studies in the metabolic activities of bacteria have required the use of media of definitely known ingredients. These synthetic fluids have been extensively used in the study of the tubercle bacillus.

The above must suffice in accounting for the prodigious labor expended on the subject of the culture of bacteria. However, in spite of the specially devised media, pathogenic bacteria decline in virulence, some rapidly, others more slowly. With continued cultivation during years, a complete loss of virulence results. Associated with this change there may be a loss of flagella, of capsules, of spore-formation and pigment-production. Pneumococci which have lost their virulence differ from the virulent strains in not being dissolved by taurocholate of soda. The decline of virulence is well illustrated by the tubercle bacillus as it appears as a function of time with certain marked exceptions. The following table illustrates both facts:

Culture designation	*Artificial culture begun*	*Date of test on guinea pigs*	*Virulence*
Bovine 1	December 1894	1931	Fairly high
Bovine 3	April 1897	1931	Nearly lost
Bovine 21	December 1926	1931	Feebly virulent
Bovine 36	June 1929	1931	Nearly maximum
Bovine 37	February 1932	1931	Maximum

The remarkable persistence in the virulence of Bovine 1 is noteworthy.

It is obvious that in any experimental inquiry into the nature of diseases it is important to maintain virulence. This can be done by using small animals and inoculating them in

series so as to keep the virus in a living environment for the time being. This so-called passage of infectious agents has two drawbacks which must be kept in mind. One is the possible modification of the agent by the alien animal host. The other is some change on account of the artificial entry of the infectious agent by inoculation in place of the more normal modes of entry through the digestive or respiratory tract. The artificial culture of microorganisms may be likened to a partial return to a saprophytic existence. In the culture tube something acquired in the ascent or descent to a parasitic state is gradually lost. This, as already discussed, is some protective mechanism residing in an envelope or capsular substance or in a limited permeability of the ectoplasm. Those substances which may be regarded as aggressive and brought from the saprophytic state, such as toxin production, remain nearly unimpaired. The descent from parasitism in artificial cultures is not infrequently an ascent to more active growth. Most bacteria acquire a more luxuriant growth in cultures as if some restraint were gradually thrown off. The bovine race of the undulant fever bacillus, requiring at the start CO_2, gradually dispenses with this need. Certain strains of tubercle bacilli capable of starting only on a special medium multiply luxuriantly on ordinary glycerinated culture media later on.

In regard to the second objective, the modification or reduction of virulence, we may say that Pasteur introduced this concept while engaged in the production of a vaccine for protecting animals against anthrax, a devastating disease of sheep, horses, and cattle which is usually acquired on pastures. Although, as stated above, all bacteria sooner or later become avirulent, Pasteur used an accelerating and more reliable method by exposing anthrax cultures to a high, rather dysgenetic temperature of 41°-42° C. After a certain exposure to this temperature animals could receive injections of the

living culture without more than a local swelling. Races of graded virulence can be produced by varying both temperature and time of exposure. The reduction in virulence is transmitted to succeeding generations of bacilli. In attempts to modify bacteria various poisonous substances, such as arsenic and chrome salts, have been added in at first very small and later gradually increasing quantities to culture fluids. A slow adaptation with certain morphological changes took place.

Profound changes in virulence have been observed when certain bacteria were introduced into alien hosts, usually small laboratory animals, and a series of inoculations carried on from one animal to another. This method was introduced by Pasteur. His thesis was that so-called passages through one host species might gradually raise virulence while passages through another might lower it. This principle was developed in his studies with rabies. Passing the natural virus of rabies as obtained from dogs through a series of rabbits, the virus gradually became more virulent for rabbits but less so for other species and in fact it lost its virulence more or less completely for man. Perhaps the most surprising phenomena in the domain of variation and adaptation were manifested in the study of trypanosome diseases in experimental animals, chiefly mice. This field was developed largely by Paul Ehrlich and his associates and pupils. In treating mice with organic compounds of arsenic, races of trypanosomes appeared in the blood of these mice which were immune to such drugs. They were drug-fast, as Ehrlich called them. This character was maintained in certain experiments for several years; in others it declined and disappeared much faster. Such races under the influence of arsenic compounds in the mouse's body became thereby not infrequently immune to other substances, such as antimony. In other words, certain correlative changes might also occur. Trypanosomes in mice treated with immune sera

became resistant to these antibodies so that injection of serum no longer protected fresh mice. These flagellates might even become immune to such sera in the test tube. This capacity of drug-fastness has also been observed among pneumococci. The loss of an important morphological structure in trypanosomes, the blepharoplast, which led Hartmann to establish the group Binucleata among parasitic protozoa, may be brought about by passages of the trypanosomes through a series of chemotherapeutically treated animals. When these defective organisms are taken up by the intermediate host, certain flies, the blepharoplast reappears. Kudicke states that passage through as many as 115 normal mice did not restore the blepharoplast lost through the influence of pyronin.

Some twenty-five years ago bacteriologists became interested in certain suddenly appearing variations among individuals of the same culture. These were called mutations. The term arose as the result of discoveries of similar suddenly appearing variations among higher plants. De Vries, the pioneer student of this phenomenon, distinguishes ordinary variability from it as follows:

"Die gewöhnliche (fluktuirende) Variabilität kann auch bei dem schärfsten Anhalten der Selection nicht zu einer wirklichen Ueberschreitung der Artgrenzen führen, viel weniger noch zur Entstehung neuer konstanter Merkmale.

"Jede Form welche durch Neubildung einer neuen Anlage entstanden ist, sollte als Mutation, jede andere, welche ihre Eigentümlichkeit nur einer Umprägung vorhandener Anlage verdankt als Varietät aufgefasst werden."

Among bacteria one form of mutation is the sudden appearance of new physiological characters. In the first observation of this kind, Massini noted that colonies of *B. coli* on agar impregnated with acid fuchsin appeared at first as white mounds but, after a variable period of days, small excrescences

or knobs appeared on the surface of the colony which were red in color. This was due to the appearance of a hitherto unrecognized function, that of fermenting saccharose, in the bacteria forming the knob. Many other forms of mutation were described after Massini. The change frequently took the form of two different types of colony on agar plates, one translucent, the other opaque, or one rough and the other smooth. The split occurred even when single bacteria had been obtained to start fresh subcultures. Mutations may be upwards or downwards. Bacteria may exhibit new characters, or certain ones may disappear. An easily produced mutation downwards affects certain races of *B. coli.* These races have a demonstrable capsule or secreted envelope which shows itself in the syrupy and viscid character of the mass growth. If such bacilli are grown in the form of colonies starting, presumably from individuals, on agar layers or plates, and sufficiently spaced so as to be at least 1 cm. apart, there appear within a few days outgrowths or films from the periphery of the colony which simulate the pseudopodia of amebae. These outgrowths are thinner than the main colony. They are made up of bacteria without capsules and of greatly depressed virulence. Sera produced by injecting rabbits with the (a) or original colony type protect against the (b) type or outgrowth form, but the reverse does not hold. The inference, well supported by various tests, is that in the outgrowth the capsule disappears, for the mass of bacilli is no longer viscid or mucoid, and that the lost capsule is the seat of the protective function in the animal body.

In recent years the concept of mutation among bacteria has entered a new stage. The studies giving origin to the advance centered about the three races of cocci associated with pneumonia in man. The pneumococcus formerly regarded as one homogeneous species was split into three distinct varieties

when the various serological tests were systematically applied. Later the distinction among these three races was shown to be due to a carbohydrate or polysaccharide which was evidently associated with the capsule. Each race produced a different sugar which embodied the specific serological character of the race. Furthermore, each race or variety could be split into two minor races, one with the capsule, the other without it. The latter lost certain properties with the capsule, among them much of the original virulence. The so-called specificity disappeared with it, for the remaining "protein" fraction of the three races was the same. In 1928, Griffith reported an unlooked-for capacity of these three forms to become transformed one into the other following certain manipulations. Thus the capsule-deprived, so-called R form could be converted into one or another of the other S forms if dead bacteria of the desired form were injected with it into mice. In other words, the I-S form could be converted into the II-S form through the I-R stage with the help of dead II-S forms and the animal body. Later Dawson and others were able to make the transformation or conversion in the culture tube without the intermediation of the animal system. Tentatively at least, one would ascribe the capacity to become transformed to a latent capacity of the pneumococcus to form the specific substance of any one of the three races under given conditions or stimuli. Certain other bacteria, among them *B. coli,* failed to become modified under these conditions.

We must postulate for the unicellular parasites the possession of an indefinite number of capacities or *Anlagen* which enable them under suitable stimulation to develop characters and functions not recognized before. The plasticity of the disease-producing unicellular organisms leads us to the inference that all were once free-living. So far as we know, some

saprophytes may develop into parasitic or invasive types quite readily, others may require long periods. Some may have been handed down from ancestral host types to man and the higher animals, with whose fate medicine is at present chiefly concerned.

In the adjustment of free-living saprophytic forms to a parasitic life in immediate conflict with living hosts, life cycles may require fundamental changes. Endogenous spore-formation so frequent among free-living bacteria and representing a definite cycle is not known among parasitic forms. The exception of the anthrax bacillus has been referred to and is only apparent for this bacillus is scarcely on the threshold of a parasitic existence. As pointed out by Koch, it does not form spores within the body but only after discharge in a suitable environment. Infection takes place through the ingestion of spore-containing food on pastures. The best known and widely disseminated spore-producing non-pathogenic bacterium is the so-called hay bacillus. It is a strictly aerobic type. The bacilli after the germination of the spores multiply abundantly in liquid media for about eighteen to twenty-four hours. During this period they are in active motion. Responding probably to the exhausted condition of the fluid medium they rise to the surface, become motionless, and form a thin papery pellicle. In this condition a spore is rapidly formed in each bacillus and the body of the bacillus finally undergoes autolysis. The spores settle to the bottom of the fluid awaiting transfer to fresh nutritive media for germination and a repetition of the cycle. The spore-formation requires oxygen, for when the culture is confined in a sealed space this does not take place. The anthrax bacillus has a similar cycle in nutrient media but it is not so sensitive to oxygen limitation.

The other disease-producing bacteria which sporulate—among them tetanus, malignant edema, and blackleg in cat-

tle—are not true parasites. The spores are not produced until postmortem anaerobic conditions have been established. Tetanus is dependent on association with other bacteria and dead tissue in wounds for inducement to multiply. Similarly malignant edema and blackleg are dependent on injury to tissues. Until recently the bacillus of botulism was not known to multiply within the body at all. The toxin is developed under anaerobic conditions in foods and it alone is responsible for the injury inflicted. The recent finding of spores in the tissues of certain animals does not of itself prove multiplication.

Supported by such facts we are justified in assuming that some of the existing parasitic forms may have sacrificed spore production as a hindrance to a developing parasitic state, and to have strengthened their defensive mechanism through the secretion of capsules or some modification of the ectoplasm towards a less permeable state. Certain groups of bacteria, among them the acid-fast types which include the tubercle bacillus, may have left behind a mycelium stage which appears now and then among the bacillar type as a branching threadlike form. Some forms, such as *Actinomyces* break up in the tissues into very short segments which represent the final parasitic stage. It has been claimed by some in recent years that the bacteria instead of representing final lower stages in the evolution of parasitism of higher forms may themselves break up into forms invisible microscopically and small enough to pass through filters which retain visible forms. Notably the tubercle bacillus has been regarded as producing ultravisible forms. However, many experimental tests have failed to bring conclusive evidence of the existence of such a stage.

Not only may it be taken for granted that parasites have had free-living ancestors in the more or less remote past, but

there is ample evidence that after the parasitic stage had been reached, modification and adaptation went on in different host species. The host, as it were, gradually put a fairly indelible stamp on the parasite. As we have seen, there is scarcely a parasite, either as worm or protozoon or bacterium or ultravisible virus, of which several or more varieties or races are not known. They point to some ancestral, more generalized type. The descendent races may still be somewhat plastic or they may have lost all unused functions and are now incapable of living in more than one host species. It may be regarded as doubtful that at the present time any new parasites are being gradually developed from free-living forms, but the possibilities inherent in the shifting of existing parasites to new hosts have not been exhausted.

VII

THE SURVIVAL OF PARASITES AND MOVEMENT FROM HOST TO HOST

ANIMAL RESERVOIRS

IT HAS been stated that the final requirement of a self-perpetuating parasite is the capacity, after resisting destruction in the aroused, reacting host, to have a way or mechanism for reaching another host individual. This capacity actually exists in all bona fide diseases which maintain themselves over long periods of time. The more highly balanced the parasitism, the more effectively carried out this fourth requirement. Coming from the former host in which the cellular protective machinery and the various antibodies have been raised to a certain level, the parasite must likewise have been stimulated to develop its protective capacities. In the fresh host, the low initial resistance gave the parasite the opportunity to multiply, but towards the end, all protective devices must have been again assumed. In this stage the path towards another host is open. Protection needed during this passage may or may not be identical with that acquired against the host tissues. Actually we are unable, owing to the minuteness of many parasites, to analyze their condition in transit. In what follows the stage of discharge and the stage of transmission are discussed together.

Among the sporozoa, the formation of dense envelopes about the spores; among still lower forms, prompt encystment are well known devices. Among diseases in which the virus finally multiplies in skin and mucous membranes the discharge is easily accomplished. In smallpox, the virus mul-

tiplies in the deeper layers of the cuticle and eventually destroys the cells. These form a crust in which the minute parasites are buried and ready to become disseminated when the crusts are shed. In other diseases similar lesions lead to preservation and discharge of the microbes.

Among the group of septic bacteria such as the streptococci and staphylococci, the resistance of the host forces them to multiply in restricted places, among them the lymph nodes. Here the resisting process is complicated and modified according to the degree of initial immunity of the host. An invasion of leucocytes from the blood partly digests the primarily reacting local tissue after this has been walled off from the normal tissues, and the softened mass breaks through outwardly and discharges its infectious material as pus. The danger in such diseases is the inward discharge of the pus and the resulting establishment of new foci or abscesses. It is probable that the bacteria in such closed abscesses are protected from the blood which becomes increasingly charged with antibodies. This unstable relationship changes from individual to individual and makes prognosis difficult and uncertain. The abscess may be looked upon as both a protection and a menace to the host. The outcome depends upon location of the abscess as well as on the capacity of the individual host to keep the parasites localized and discharged as promptly as possible.

The usual multiplication of certain bacteria on the mucous membranes and their occasional penetration into the closed confines of the tissues as aberrant movements has been described. Such invaders may be considered lost to the race of bacteria, and only those living on and in the mucosa are the ones which carry on the disease in the form of relapses and persistent chronic irritation, as well as conveyors of infection to others. The tubercle in tuberculosis may be considered an

abscess so far as the survival and subsequent dissemination of the bacilli are concerned. The internal cellular contest is, however, not the same as in ordinary abscesses.

The well known avenues and vehicles used by parasites to reach a fresh host are immediate contact of hosts, the air, food, water, and insect vectors. In addition to these vehicles and routes, the perpetuation of parasitism is assisted in some degree by another mode of transfer through the egg and by way of the intrauterine route during gestation. It was Pasteur in the 'sixties of the nineteenth century who first called attention to the passage of parasites in the egg to the succeeding generation. At this period, pébrine, a sporozoan disease of silkworms, was greatly injuring the silk industry of France. He observed that the ova of the infected moth might or might not contain the spores of the parasite. A microscopic examination of the chrysalis, the adult, or the ova served to detect their presence. The entire progeny was then destroyed. The emphasis was thereafter placed on the ova or *graine* in securing a generation free from disease. Since that time numerous instances of the transfer of parasites in the ovum have been recorded.

In one form of piroplasmosis (Texas fever), the protozoan parasite of the red corpuscles of the bovine blood is drawn out of the blood by a species of tick which in turn passes it in the ovum to the succeeding generation of ticks. These when attaching themselves to the skin of a fresh animal and beginning to draw blood inject the inherited parasites, thereby completing the cycle.

In birds and lower animals the opportunity for parasitic forms to use the ovum as a vehicle to pass from one host generation to another is obviously enhanced by the large amount of reserve food material stored with the ovum. In chickens a peculiar ovarian disease due to a relative of the paratyphoid

group of bacteria leads to the inclusion of this organism in the egg and the subsequent appearance of the disease in the newly hatched chicks. In the latter it appears as a local or a generalized disease with foci in many organs, especially the lungs, and lesions of the intestines. The few chicks that remain alive and reach maturity may go through the same process of ovarian disease. The transfer of the microbe in the yolk to the next generation is made possible by this process. In mammals the transfer of infectious agents to the embryo may be accounted for by localized disease of the uterus, or by a passage through the placenta from the mother's circulation. In this way rare cases of congenital tuberculosis, syphilis and perhaps leprosy appear at birth. Quite recently it has been observed that certain nematode parasites, which enter the body by way of the skin or the mouth, migrate in more or less circuitous paths to their final habitat in the intestines. Some of these, literally losing their way, may penetrate into the uterus and the fetus and appear in the intestines of the young soon after birth. In general the transfer of parasites via the ovum and embryo is restricted. The uterine cavity is well protected both from without and within. The blood, in which parasites must travel to enter the uterus, is a highly antagonistic fluid. However, this mode of transfer must be reckoned with in all attempts at complete eradication of any form of parasitism in domestic animals. Some rare cases of transmission after a period might act like a single spark among combustibles in an increasingly susceptible population.

The maintenance of living agencies of disease must be looked for chiefly in the close association of old with young, of one generation with another. The evolution of parasitism has gone on under the dominating influence of this principle. To study the effect of close association upon the early transmission of parasitism the best objects are either animals or

primitive human groups. Modern sanitation and preventive medicine have placed certain routine obstacles in the way of direct transmission which prevent our visualizing the principle in its full operation in the human subject. It has been stated that in his early studies on malaria in Africa, Koch called attention to the universal infection of children in African village groups. They all had large spleens and parasites in the red blood corpuscles, but they appeared well. His inference was that in a partly immunized group malaria became a childhood disease. This might mean either that adults were entirely free from infection and that children were the chief, if not the only source of the infecting agent, or that adults were simply carriers after having overcome the active disease.

In view of the relative susceptibility of the new-born and assuming the almost immediate exposure after birth to infectious and parasitic agents carried by the parents and in the environment among groups of animals and in primitive human society, we may well ask what stood in the way of a more or less complete wiping out of the new generation. What is the machinery set up by nature to protect the larger organisms against the minute forms? In epidemics among animal populations, the first impact of a new virus or parasite is against individuals of all ages. That some survive is probably a matter of chance, due in part to immunological factors overlapping from other diseases, in part to genetic individual differences. The extinction of so many species in past geologic ages is best explained as a result of freshly introduced parasitism. The second impact, after the first has been met without extinguishing the population, is against the young. In all epidemics of domesticated populations of small and large mammals and birds, the chief morbidity and mortality is among the young. This gradually tends to eliminate the

weak variants and develop a more and more robust population capable also of meeting new and the increasing virulence of well established parasites.

It has been known for many years that certain protective substances, called antibodies, pass from the mother to the fetus in the placental circulation. For example, experiments have shown that the new-born guinea pig has received from the mother, who had been treated before pregnancy with toxin-antitoxin mixture, enough antitoxin to enable it to resist the injurious action of a certain amount of diphtheria toxin. This protective substance gradually disappears and is lost after two months. Among a population in which certain diseases constantly occur, the young receive some protection in the manner described. Among the ruminants the placenta is impermeable to antibodies and nature has provided another route. The mammary gland of the cow, for instance, being inactive for several months before the birth of the calf, stores antibodies received from the blood, and the first milk or colostrum taken by the new-born calf gives the young the antibodies which are promptly absorbed from the digestive tract into the blood. This absorption of antibodies lasts only one or two days. Moreover, after the stored milk has been exhausted, the normal milk contains very little of the blood antibodies—probably not more than one-fiftieth to one-one-hundredth. In this group of animals the induction of protection is a matter of the earliest twenty-four to forty-eight hours of life and the protection itself lasts one or more months. The significance of this transfer of antibodies can be determined by withholding this early colostrum and feeding ordinary milk from another cow. In large herds in which various kinds of infectious agents have accumulated three-fourths of all calves thus treated become ill and may die within thirty-six to forty-eight hours. Or they may live and develop various

ills, such as arthritis, nephritis, septic infections of the umbilical cord, and various intestinal disturbances. These diseases are produced by common bacteria in the environment of the cow, among them *B. coli,* but the cow is immune to them. She has protective substances in her system, some of which the calf failed to receive when the first milk was withheld. These bacteria are only potentially pathogenic. Bacteria which are incapable of producing disease in the mother cow even under certain depressing conditions are also incapable of multiplying in the calf. There are therefore groups of bacteria which even the unprotected calf can destroy and groups which may produce disease but are readily kept under control by the natural process described.

The possibility of certain, chiefly infectious diseases being transmitted to the offspring via the ovum and the uterine circulation is thus definitely established; similarly the regular and immediate exposure of the young to infections carried by one or both parents. To counter the dangers thus operating, the intrauterine or intramammary passage of protective substances or antibodies is also in operation. The resultant is an elimination of the weaker and a fortifying of the stronger progeny by a kind of natural vaccination under the protection of the passively acquired antibodies. This dual machinery might explain in part the geographic immunity of populations who have lived in contact with certain diseases through indefinite periods. Genetic factors favoring the host would also come into play. Latent unused capacities would be stimulated to activity until they became physiological. At the same time it must be admitted that such latent capacities may not exist or be developed to a degree not fully protective. Such populations would decline and die out.

The transmission of infectious and parasitic agents directly from mother to young through the ovum or *in utero* repre-

sents only a minute by-pass of the many channels through which they go from one individual to another. It would leave a gap in this discussion if there were omitted reference to the immense amount of labor expended in tracing the transmission of disease germs and blocking their way. The newly developed science of bacteriology was chiefly concerned for many years in this study—notably the tracing of infectious agents from the digestive tract into water, soil, and foods. The cycle of infectious agents involving entrance into the respiratory tract has also received much attention. The means to break this link have met with only slight success except in those diseases whose victims could be hospitalized. Many infections of the upper respiratory passages are not severe enough to limit the movements of patients. The steady concentration of populations in cities has kept this mode of infection not only open but more intense from year to year. Much time has been devoted to determining the aerial modes of dissemination of the tubercle bacillus. Here two vehicles are used. The minute, even microscopic droplets of mucus and dead tissue coughed up may remain floating for a short time and be inhaled directly. The dried sputum ground into dust may also enter the lungs and produce infection at a distance from the patient.

In the development of the economic aspects of our civilization, while medical and sanitary science on the one hand have been making prodigious efforts to suppress this fourth link of the parasitic cycle, man on the other hand, even though in part unaware, has also made prodigious efforts to distribute disease. All means of rapid communication add to the dangers of bridging the natural chasms which interfered with the planting of disease in a primitive society. Even the more or less altruistic efforts of the medical art in hospitals before the modern bacteriological era produced epidemics of

puerperal fever, erysipelas, and the like through faulty manipulations and ignorance.

A most important form of transmission of parasites from host to host, to which reference has been repeatedly made in these lectures, is that engineered by insects and arachnids. So many have been shown to be active transmitters of worms, protozoa, bacteria, and ultravisible viruses, that it is safe to conclude that all such animals which live upon the human and the animal body or merely visit them to abstract food, usually in the form of blood, are potential if not actual promoters of disease. The arachnids or ticks have been shown to be formidable enemies of the higher animals in their capacity for transmitting both protozoan and ultramicroscopic organisms. Among these are the different piroplasms or malarial diseases of domesticated animals prevailing in all countries. The mode of transfer varies from insect to insect and according to the nature of the parasite transmitted. The relation between the large host, the insect or arachnid, and the minute parasite may be so highly adapted and specialized that the disease due to the parasite can be set in operation only on one host and that such disease cannot exist without the particular insect transmitter. The protozoan parasites causing the various forms of malaria in man, mammals, and birds belong to this group. The same is true of the helminth parasites, the filaria. Of the many diseases due to filtrable viruses brought to light in recent years, a fair proportion is subject to insect transmission. Among them are such redoubtable plagues as yellow fever and typhus fever.

In the protozoan group of parasites, the complex life cycle of the microscopic parasite has been apportioned in part to the larger host, in part to the insect or arachnid. The latter take care of the important reproductive phase during which sexual dimorphism is manifested which leads to an abundant

progeny ready to be injected into the larger host. In the blood stream of the host a copious asexual multiplication takes place before the parasite is ready to be drawn out of the blood by and into the next insect feeding on the host. Both types of multiplication combined provide a large progeny of the microscopic parasite. In the insect vector, the movement of parasites is standardized, as it were, and forced into one channel in the absence of which the disease cannot spread. In the evolution of this type of parasitism the minute parasite probably belonged originally to the insect since the most important phase goes on in it. The entry into the vascular system of the larger host may be regarded as a bypath assisting in the asexual increase in numbers. In due time this bypath became a necessary link in the life-cycle of the parasite.

Attention has been called to the dangerous diseases of man and animals caused by protozoa known as trypanosomes which multiply in the blood stream. They are introduced and perpetuated by certain biting flies. The upkeep of diseases by insects is largely a tropical and subtropical phenomenon. They are the main obstacles to the opening of tropical countries to northern races.

An important modification of the normal cycle of certain parasites, uncovered by medical research, is the very long drawn-out stay of the parasite in the host after outward signs of parasitism have disappeared. Each group of parasites has its own way of maintaining itself in what is now a hostile environment. Among the bacteria and probably certain ultramicroscopic forms, the survival takes the form of an infection of the mucous membranes, among them the throat and sinuses of the head, the intestinal tract, the bile duct and gall bladder. Individuals harboring bacteria long after the disease due to them has subsided are known as carriers. The bacillus of typhoid fever is a notorious instance of survival in the recov-

ered system. Public health officials have traced many small epidemics to this source. It is well known that the diphtheria bacillus may remain in the upper air passages after full recovery of the carrier. The simplest explanation of these occurrences is that the bacteria concerned are parasites of the mucous membranes and that disease is a side product following accidental invasion of the body tissues. This invasion furthermore is due to some unbalance of the host-parasite equilibrium, either primary or resulting from temporary loss of resistance on the part of the host or some increase in virulence of the bacteria. Among the protozoan parasites prolonged residence in the same host, when fresh infection is excluded, is almost the rule. The piroplasms of Texas fever have been found in the blood of cattle five years after the last opportunity for exposure to ticks. Similarly the malaria parasites tend to survive one or more years in certain hosts. In these prolonged cycles there is very little multiplication going on, for the microscope fails to detect it. On the other hand, injection of such blood into a fresh susceptible host reveals the parasites, for multiplication and consequent symptoms of disease follow. Now and then the resistance of the carrier himself has been sufficiently reduced by exposure to give the parasite a brief opportunity to multiply and produce what is known as a relapse.

The occasional wandering of parasites from their normal hosts to alien species has been discussed under abnormal and incomplete cycles. To the human race these cycles are of significance since the animal world is subject to a variety of parasites, some of which are capable of multiplying in man. When this occurs with the useful, domestic animals the problem how to deal with such diseases is a difficult one. As a rule the cycle is not completed in man and he therefore does not transmit the disease to other human beings. The relation

of man to his domestic animals as well as to certain small predatory animals, such as rats and mice, is quite intimate and a brief statement of human diseases coming from them may be of use in assisting in their suppression.

Glanders is a dangerous and frequently fatal disease, sporadically encountered in man, which is exclusively carried by diseased horses and their relatives, the asses and mules, although it is inoculable into a larger number of other animals. Before the entrance of the automobile into industrial life, glanders was not uncommon. In fact twenty-five years ago there was a fair amount of this disease traveling daily over our city streets. It caused the death of a number of scientists and their helpers in the laboratories. Medical literature is replete with details of cases in men in contact with diseased horses, especially during war periods. The open disease in horses is readily diagnosed and the earliest stages brought out by mallein. Health boards were quite alert in stamping out the disease by killing open cases and watching those which reacted to mallein. Today it is fairly well suppressed, thanks to the diminution of horses and the activities of health agencies. In man the disease takes on protean characteristics from chronic lesions of the skin lasting twenty years to acute septicemic cases fatal in a few weeks. It has been repeatedly and thoroughly monographed in medical serial publications, so that there is no difficulty in getting acquainted with the human side of the disease.

The relation of rats and certain rodents to bubonic and pneumonic plague was established fully a generation ago. Since then sporadic outbreaks of this disease have made themselves felt in widely separated territories, and during such occurrences, plague rats have regularly been found in the infected territory. In the far west of the United States other rodents, such as ground squirrels, have been found dangerous

carriers. The microbe is one of a large group infesting the respiratory tract of the lower animals but singled out by its fierce onslaught on the human species. It is well known that the bubonic form of plague is not readily passed from man to man, probably owing to the fact that the mode of introduction of the human virus into a fresh wound would rarely occur. The diseased rat aided by the bite of the rat flea provides the necessary mechanism between rat and man. On the other hand, the pneumonic form may be transmitted like other respiratory infectious agents directly. Originally derived from a rodent of woodchuck type, it becomes a genuine human plague. The Black Death of the Middle Ages is generally identified with the pneumonic type.

Since the World War a disease has been observed in nearly all parts of the world which is similar to Malta fever first detected on the island of Malta. There its source was definitely traced to goat's milk. In the northern climates the new disease, now known as undulant fever, was traced to contact with swine and their products and to cow's milk. Three distinct races of the bacillus have been associated with this disease, a caprine, a porcine, and a bovine race. These differ so slightly from one another that it required some years to dispel the confusion created by this close similarity. In our country the porcine variety has been the chief cause.

Tularemia is a disease of rabbits which is destined to play a more conspicuous rôle in the future since it appears to be spreading from the west into eastern States. It occurs among hunters and others handling the flesh of infected rabbits. In man the inflammation starts from some cut or laceration of the hands or arms and moves to the lymph nodes which may become abscessed. The mortality is high. The cause is a small bacillus which produces abscesses in rabbits.

Rat-bite fever has been definitely associated with a minute

spiral bacterium which is introduced in the saliva of the rat during the bite. The human disease has been recognized in different countries as a relapsing fever.

We are indebted to the rat for another characteristic human disease, which like rat-bite fever has a world-wide distribution. Infectious jaundice has played a prominent rôle among soldiers in various wars of the nineteenth century. The relation of the rat to this disease and the causal agent were demonstrated by Japanese scientists in 1916. The disease is characterized by sudden onset of fever, severe muscular pains, and jaundice usually on the fourth day. A second elevation of temperature, known as after-fever, may occur after subsidence of the first febrile reaction.

The anthrax bacillus has always been a classic to the bacteriologist since it was the first microbe actually seen in the blood of affected animals and also the one with which Koch over fifty years ago began his career and Pasteur gained recognition through his now celebrated anthrax vaccine. The bacillus is quite a universal agent, since it attacks horses, sheep, and cattle, and perhaps many wild species on pastures. The dangerous factor in its make-up is the spore which survives in a dry condition many years. I have myself kept dried spores eight years and found them making abundant growth overnight when placed in suitable culture media. The wool, hairs, bristles, and hides of domestic animals are dangerous vehicles of these spores and governments have been trying for many years to devise successful disinfectants which will not materially injure these articles of commerce and industry. Inasmuch as there is no evidence that healthy animals carry the infectious agent the danger to human beings is very slight, provided the agencies of governments do their duty in not allowing the products coming from animals dead of

anthrax to enter commerce at all or at least without adequate disinfection.

Rabies, like anthrax, has a wide spread among animal victims and almost all mammals tried have been found inoculable. The real distributors, however, are limited to the species that bite, the dog and wolf. Casual transmission by other rabid animals may occur through their saliva but this is rare. There is no other disease known with such inclusive powers to infect and cause fatal disease. Here also Pasteur's genius has provided a defense in his method of vaccination. The increasing extent and intensity of rabies among dogs in densely populated territories over the entire globe have stimulated efforts to provide some protective measures for dogs with a modified Pasteur vaccine. Such procedure is now being tried in certain communities but without the scientific centralized oversight which such an important practical experiment demands. The great international importance of rabies is expressed in the International Conference on Rabies held in Paris in 1927, during which all the various procedures used on human patients were discussed and scrutinized.

Another widespread group of bacteria producing septicemic and enteric diseases in animals and not infrequently group outbreaks in man is the paratyphoid group including *B. enteritidis,* related on the one hand to the typhoid bacillus, on the other to certain races of *B. coli.* In man this species of bacteria is most frequently associated with acute gastrointestinal upsets, leading in rare instances to a fatal outcome. In another group of cases the disease simulates typhoid but is less severe, less protracted, and rarely fatal. Where man acquires this infection has been the subject of research for nearly forty years and enquiries are still going on. The reasons are not far to seek. The paratyphoid group of bacteria produces enteritis in cattle and swine, and abortion in mares.

It produces epidemics among rabbits, guinea pigs, and mice in our laboratories, and in wild rats. It is represented by several distinct serologic groups which break up into minor subgroups. In the smaller animals several races may infest the same species at the same or different times. Certain group outbreaks in man have been definitely traced to rats and to veal, horseflesh and pork, when not sufficiently cooked. It is not improbable that the strains infesting the larger animals are distinct from one another but that the smaller animals are susceptible to all. It may be that the rat is an exception and cultivates its own variety.

Much has been written during the past twenty-five years on the significance of bovine tuberculosis to the human race. The transmission of the bovine tubercle bacillus occurs almost exclusively in cow's milk. In the second and more advanced stages of the bovine disease, the udder may become the seat of tuberculous processes due to the escape of bacilli temporarily circulating in the blood into the milk ducts as the result of some focus breaking down. About one to two per cent of tuberculous cows have some tuberculous foci in the udder. Cows in very advanced stages of the disease, when emaciation has set in and the disease has become generalized, may discharge a few bacilli in the udder. The cow's chief form of tuberculosis is pulmonary. The cow coughs up particles of caseous material and mucus impregnated with tubercle bacilli. This coughed-up material is chiefly swallowed but some is thrown out during coughing, otherwise it would be difficult to account for the preponderating pulmonary disease of the cow herself. The swallowed bacilli are discharged in the feces and when the milking is not guarded by preliminary cleansing of the cow, some of these bacilli may find their way into the milk pail with fecal matter.

A disease of startling possibilities but restricted by advancing agriculture is the Rocky Mountain spotted fever which first came to the notice of medical science in the 'nineties of the past century. The human disease is an acute febrile disease, characterized by an eruption of spots, varying much according to the severity of the attack from bright red to purple. The mortality is high. In 1903, 121 cases had been collected, of which 84 were fatal. The immediate incitant is a tick, the bite of which injects the virus. This mode of transmission accounts for the non-contagiousness of the human disease, observed by all local physicians. The demonstration of the infectivity of the wood tick was given by Ricketts in 1906. He also was able to induce the disease in guinea pigs, which animals in turn infected ticks placed on them. He furthermore showed that the virus may pass to the ova of the infected female tick and thence to the next generation. Ten years later, Wolbach demonstrated the presence of minute bacteria-like organisms in the vascular lesions of human and animal victims and in the infecting tick.

Psittacosis, a disease which affects parrots, has been known for many years to produce family epidemics among human beings following the introduction of fresh birds into the household. Only recently has the nature of this disease been cleared up. It is due to a filtrable virus, that is, an ultramicroscopic organism. It is highly dangerous to man and several investigators have lost their lives while studying the disease. The virus is discharged in the nasal secretions and feces of the sick birds.

Our relation to animal life under the present urban and rural conditions of living is made quite intimate through the consumption of raw cow's milk. I have already mentioned the presence of tubercle bacilli in tuberculous udders and of *B. abortus* in the udders of a small per cent of cows which

have aborted at some time and are carriers of this species. A third potentially dangerous organism appears now and then in the udder—a streptococcus—which has been the cause of numerous large and small epidemics of septic sore throat. The sudden appearance of widespread epidemics of this disease was signalized some twenty years ago. Before that time it was probably prevalent in small outbreaks and such occurrences had been reported from England by Klein, Savage, and others. In this country the consolidation of distributing agencies and the practice of mixing the milk of a large number of cows led to the larger outbreaks. Hundreds and even thousands of cases in a single epidemic have been reported since 1910 in different cities of the United States. In a precisely similar manner, the streptococcus of scarlet fever may lodge in the udder and give rise to epidemics of this disease.

Some parasites have multiple hosts among which man may figure, as in anthrax, rabies, and glanders. The chapter would be incomplete without again referring to certain higher parasites which come under this category. The fish tapeworm, not infrequently encountered in eastern Europe, has probably established itself recently in some of the inland waters of the United States. Carried across in the intestines of some European immigrant and discharging countless ova, the parasite thus furnished the opportunity for fishes to become infested with the intermediate or larval stage. Another tapeworm (*Echinococcus*) belonging in its adult, intestinal stage to the dog has figured more or less in the medical and surgical literature of the past because the intermediate larval stage following the ingestion of ova discharged by the dog has been found in almost every organ of the human body, notably the liver in which organ large cysts develop gradually. These may break and when situated in vital spots, such as the medulla oblongata, they have caused instant death.

Another strictly animal parasite which has multiple hosts and has played a conspicuous rôle in human pathology in the past, especially in central Europe, is the roundworm, *Trichinella spiralis*. It has caused extensive local epidemics with high mortality following the consumption of the raw muscular tissue of a single pig. Trichinosis is not unknown even today when unfortunates consume inadequately cooked pork. The parasite is attributed to the pig, but it occurs in rats, and small laboratory animals have been infected successfully. All that is necessary to maintain the disease is for the pig to eat an infected rat and for another rat to gnaw the body of the infected dead pig and so on *ad infinitum*.

A subject somewhat alien to the theme discussed but of sufficient importance to warrant brief mention is the acquisition of alien infections by small animals. We have seen that the guinea pig has acquired at least three races of streptococci probably from man. Several races of paratyphoids and staphylococci are now an integral part of this animal's equipment of diseases. The same tendencies are at work in mice and perhaps other rodents. We are naturally interested in the fate of such organisms, whether they are sufficiently modified to become harmless to the original host or whether their alien qualities persist and their return to the original host is a matter of opportunity.

The fourth stage of the parasite cycle as briefly described is seen to consist of a number of diverse links beginning with the egg and intrauterine life and later brought about during lactation and through the medium of air, water, food, contacts with living carriers and inanimate objects and through insects and archnids. For some animal diseases man becomes an accidental victim without the capacity for carrying on the cycle in his own species.

VIII

EPIDEMIOLOGY

IT IS evident from what has been stated that slight changes in the physiology of microbic parasites may cause profound disturbances in the hosts to which they belong. Notably the heaping up of disease in the form of epidemics may be due to such changes. In recent years the study of the rise and decline of epidemics among experimental animal populations has brought to light interesting concrete data and specially stimulated a renewed search for such data on the great plagues of history. Before we enter upon a discussion of epidemiology in the light furnished by bacteriologic research a few glimpses into the past will emphasize some of the mysteries still to be uncovered.

Among the diseases which have left their impress upon the human race one stands preeminent, the bubonic plague. This is a highly fatal disease, due to a microbe which on entrance into the body spreads and multiplies rapidly and may be compared to a fatal case of blood poisoning or septicemia. Several types of the disease are known which differ in virulence. The bubonic plague receives its name from the swelling of the glands or lymph nodes under the skin in one or more regions of the body. The Black Death of the Middle Ages was probably a more severe type of the same disease, in which the lungs were frequently affected. Death usually occurred in three to five days. Epidemics closely resembling plague were described thousands of years before Christ and they have reappeared at longer or shorter intervals up to the present day. Among them the great pandemic, or Black Death, of the

fourteenth century stands out conspicuously and obscures more or less the earlier and later waves of the same disease.

The earliest records of what was probably the bubonic plague appear in the Old Testament: "And the men that died not were smitten with emerods: and the cry of the city went up to heaven" (1 Sam. v: 12). Numerous localized epidemics have been described by Greek and Roman authors. In Utica there remained of a garrison of 30,000 scarcely ten. Deaths occurred so rapidly that more than five hundred bodies were carried out of a single gate of the city in a single day. Other plague epidemics are described as occurring 50 B.C. in Libya, A.D. 66 in Rome, A.D. 98 in Africa and the Levant. The great plague of Galen which prevailed under Antoninus is interpreted as smallpox. The great plague of Justinian, which began in 532 in the East, circled the Mediterranean in four periods of about fifteen years each, and finally after a supremacy of sixty years disappeared, leaving formerly populous countries like deserts.

Preceded by smaller epidemics which occurred in every century since that of Justinian, came the Great Mortality of the fourteenth century. Numerous legendary statements concerning the origin of this pandemic are extant, differing widely in their accounts. But all agree in referring it to the Far East. It halted in Constantinople in 1347, where it prevailed in all parts of the city and among all classes, in the Emperor's palace as well as the hut of the poor. The Emperor's son succumbed with countless others. From Constantinople and other ports vessels carried the disease to every country of Europe and as far as the Pillars of Hercules in Africa. Countless Tartars, Saracens, and other peoples of the East had already been destroyed. Fully one-fourth of the entire population of Europe perished. Both Boccaccio and Petrarch were in their prime when the plague was devastat-

ing Italian cities. Boccaccio rendered due homage to this great catastrophe in his *Decameron*. Petrarch lost his Laura and most of his intimate friends, evidence enough that it was not merely a disease of the poor that was prevailing.

The Great Mortality was followed by other lesser incursions in succeeding centuries. Only a few stand out in relief because preserved in literature. London had been repeatedly invaded before the final and most severe epidemic in 1665. This has been made famous by Defoe who in his *Journal of the Plague Year* gives a succinct account of the events of that year. He was only five years old but the narrative is presented to us as by an eyewitness. Following armies and famine, the pestilence moved about Italy during the early part of the same century. The terrible affliction of Milan in 1630 is described by Manzoni in *Promessi Sposi*. The last great European epidemic covered the first quarter of the eighteenth century. In Marseille alone 39,000 out of a total population of 90,000 perished within a period of eleven months. Many other larger cities suffered losses in the same proportion.

Though the same scourge had appeared from time to time during the nineteenth century in epidemics especially in the Asiatic continent and in European Russia, yet in none did it gain any momentum and arouse any apprehension of its latent powers until it appeared in Canton in 1894. Thence it was carried to India where it has been epidemic ever since. At different times it invaded seaports in various parts of the world. In 1900 it reached San Francisco and threatened the rest of our country. In 1907 it was present in China, India, Japan, Asiatic Turkey, Arabia, Persia, Straits Settlements, Siam, and French Indo-China. In Africa during the same year, it was present in Madagascar, Mauritius, British South Africa, Egypt, Algeria, Zanzibar, British East Africa, and Tunis. Cases occurred in Russia and Great Britain, and on

the Western Hemisphere it was being fought in Argentina, Brazil, Paraguay, California, Peru, Trinidad, and Uruguay. Lastly it appeared in Hawaii, Australia, and New Zealand. In some of these numerous foci, the plague was epidemic; in others, represented by a few cases only.

The human mind was profoundly disturbed during the epidemic periods and the usual social bonds loosened or completely destroyed. Extant records emphasize the licentiousness of the population under the influence of this terrible disease. Human beings shunned one another. Wills were dictated by the dying from the windows of houses which the well did not dare to enter. Superstition and fanaticism cooperated in the formation of special groups of annointers and flagellants. Religious processions spread the plague. The miseries of certain minority groups of the population were intensified through the ill will of the majority. Jews were accused of poisoning the wells and persecuted.

Another acute and rapidly spreading plague of wholly different type is the Asiatic cholera. This disease was not known as an epidemic disease outside of India before 1817. At that time it spread from the rivers of India close to the frontiers of Europe. It lasted about seven years. In 1826 a second pandemic spread over entire western Europe, except the Scandinavian countries. In 1832 it overran Canada and the United States. It died out completely in the winter of 1837-1838. A third pandemic lasted from 1846 to 1863. It invaded the United States in 1853 and 1854 but disappeared in 1855. A fourth pandemic lasted from 1863 to 1875. In 1885, while working in India, Koch discovered the cause as a vibrio or curved bacterium. One severe outbreak occurred in Hamburg in 1892. This disease is limited to the intestinal tract in which the causative organism, a spiral form or vibrio, multiplies, and sends its toxins into the system, injuring at the same time the

mucous membrane. The result is an immense loss of water from the tissues of the body.

Very different from these acute, rapidly spreading and rapidly vanishing plagues was another which rested like an incubus over the world during the Middle Ages and later. Leprosy is a chronic malady lasting a lifetime. Its nearest relative is tuberculosis. It is an endemic disease in many countries today but in the past it prevailed in almost epidemic intensity in western Europe. The disfigurement of face and loss of fingers and toes, and the offensive breath made its victims outcasts in ancient times. Since the seventh century Christian and humanist sentiments became active and lazar houses were built to lodge the lepers. These houses were the forerunners of modern hospitals. This was then the only disease regarded as needing segregation and institutional care. There were many leper hospitals in Europe during the later Middle Ages. They reached their maximum in the fourteenth century. The leper was legally dead. He had no rights in a court of law and was disqualified from making wills and inheriting property. Nothing was expected of him. His sequestration was initiated by a religious ceremony.

Records of many curious regulations to govern the inmates of lazar houses framed in England, France, Denmark, and other countries are extant. In Denmark there were certain entrance fees to be paid. Inmates were to furnish their bed and other articles. Occasionally the disease attacked men of rank and they were allowed to live in separate houses. As a rule the victims were of the lowest classes, however. Some lazar houses were well endowed. Others were very poor and the inmates begged. One was supported by tolls from everything carried to sale at Chester market. Among the suggestive statements are the following: "Tainted salmon or pork to be sent to the leper house. If there was not one, it is to be

destroyed." "When a wild beast be found dead or wounded in the forest its flesh shall be sent to the nearest leper house." Kingcase Hospital had eight lepers, "who are each to have 8 bolls of meal and 8 merks yearly, and if there is but one, he has the whole." Even politics and its twin brother, graft, entered into the management of these lazar houses.

Tuberculosis is so well known and so widely advertised a disease of civilized nations that it hardly needs an introduction here. It has many of the characters of leprosy but its clinical expression is wholly different and it is far more acute. Perhaps the most striking phenomenon associated with this plague is the steady, gradual fall in mortality during the past three-quarters of a century. It is generally conceded that most individuals in urban communities are passing through or have passed through some slight disease due to minute doses of the tubercle bacillus which leads to a certain degree of resistance, if not immunity, towards any more severe reaction. Under prevailing conditions this disease may share the same fate which overtook leprosy in Europe and fall to a negligible level in due time.

Among the major plagues of the past, smallpox must not be forgotten. It is still with us, owing to a general indifference and even hostility to vaccination. Before Jenner, it was a universal disease, sufficiently dreaded to induce many people to subject themselves to inoculation with the virus of smallpox itself, for the purpose of inducing a mild attack. This was not infrequently severe and at times fatal. Inoculation was introduced from the East in the early part of the eighteenth century and supplanted by Jennerian vaccination nearly a century later.

Among the epidemic diseases inspiring fear and terror are those carried in the air and not amenable to ordinary precautionary measures. We have seen that the pneumonic plague

belongs to this class. Perhaps the only other form of epidemic disease using the air chiefly is known as influenza. This disease involves the upper air passages and secondarily the lungs. It should be mentioned that direct and indirect contact cannot be excluded. The use of unsterile eating utensils, kissing and actions carrying infection from one mouth to another or into the nasal passages must be regarded as effective. Influenza epidemics have been recorded since the twelfth century but even today the diagnosis remains uncertain until the microorganisms responsible have been definitely recognized. Within the memory of those living two pandemics have displayed their capacity for overrunning the globe, one around 1890, the other during the World War in 1917-1918. Of the two the latter was the more virulent. The speed and suddenness of invasion into a new community, its frequent occurrence on shipboard with no land connections, the immunity of strangers and visitors contrasted with the susceptibility of the natives, baffled earlier physicians and led to the doctrine that influenza was not due to a *contagium vivum,* since it moved and spread too fast. The question whether the epidemic always moved east or whether it went in other directions was actively debated. Today in spite of the etiological uncertainties such questions are no longer seriously discussed. It is generally accepted that slightly ill, partly recovered, and even normal human carriers of the virus are responsible for the spread of the infection.

Yellow fever, another dreaded disease which has prevailed in extensive epidemic waves since the earliest records in the seventeenth century, can now be satisfactorily interpreted in its various manifestations. The older epidemiologists had uncovered a number of peculiarities of this plague with great keenness and remarkable accuracy. They had no knowledge whatever or even a suggestion of the microbic factor or its

vector. In a summary of the extant records by August Hirsch in 1881, in which he gives ten closely printed pages of references to the published observations on this plague up to the date of writing, we encounter a surprising number of details, all of which converge on the one factor, mosquito; yet among the many hypotheses proposed none came within hailing distance of this insect. These theories concern themselves largely with vegetable decomposition. One assumed that the crowded holds of slave ships and the decomposing bilge water were the source of the "poison." Hirsch says: "Hypotheses as to the nature of the yellow fever poison, leaning sometimes to one side, sometimes to the other, have exhausted the ingenuity of the profession without advancing our knowledge by a single step." His "one side and the other" refer to two theories: "whether namely, the disease-producing factor is to be sought for among those decomposition products themselves, or in whatever sets the decomposition agoing, or in other organic (or organized) forms standing in a certain relation to the processes of putrefaction." The terrifying character of yellow fever epidemics lay in their wide dissemination from obviously endemic centers. The home of yellow fever is a limited strip of the west coast of Africa. Coming over in slave ships it settled in the islands of the West Indies and Mexico and extended into the South American continent. From time to time summer epidemics visited the South and the North Atlantic coast of the United States extending as far as New England but diminishing in intensity and frequency northward.

The subjects discussed among students of the yellow fever problem prior to any accurate information concerning its causative factors indicate a close approximation of the data to the insect vector. The outbreak is never sudden. It starts with isolated cases. The disease may remain restricted to a

certain urban quarter, even to a single block or a single house or ship. Epidemics greatly vary in length. It is a disease of the tropics and of hot seasons. Frost stops it, but it may survive the winter. It is influenced by the winds. Hot south winds favor it; cold north winds check it. It seldom leaves the seacoast or the banks of navigable rivers. It has a limited altitudinal range. It is an urban disease and haunts low and filthy quarters of seaports. Geological characters of the soil are of no account, nor are malarious conditions of soil relevant. "Even the most intimate kinds of contact such as the healthy and the sick sleeping in one bed, the attendance of physicians and nurses on the sick, the use of unclean linen, clothes, or beds of yellow fever patients, post-mortem examination of their bodies, and the like, have in no wise contributed to the spread of the disease" (Hirsch). Emphasis must be placed on the word *spread,* since wounds at autopsy may produce the disease. All these facts bearing on its natural history agree with the peculiar habits of the mosquito which transmits the filtrable virus. They illustrate in a conspicuous manner the service rendered by medical science in bringing into full view the fourth or transmitting phase.

Typhus or spotted fever is associated with "war, famine and misery" and is a standing challenge to the human race to eliminate these causes everywhere. The seventeenth and the eighteenth century were prolific in epidemics of this disease. Unlike the plague or influenza, it does not spread in pandemics but remains localized. It appeared as a result of overcrowding and unsanitary conditions, which were largely due to famine on the one hand and on the other to the disseminating activities of armies and returning soldiers. The conditions favoring this plague were clearly defined by early physicians but no hint of the underlying etiological moments appeared in the voluminous records. Though conditioned by

physical wants and privations it nevertheless did develop independently of these in invading even the courtroom and frequently attacking doctors and nurses. It was apparently independent of telluric conditions, although it was generally agreed that the coming of spring with greater freedom and outdoor life controlled the disease. The discovery that the body louse is responsible for carrying the virus from victim to victim explains and clears up all conflicting observations and agrees with the determination that overcrowding and filth are favoring factors. The hunger typhus obviously is accounted for by the depression of vitality in the presence of the virus. The appearance of localized epidemics when they could not be referred to any recognizable case of the disease is now explained by the existence of recovered and immune individuals still carrying the infectious agent in their blood. The louse is an obligatory parasite of the human body. The very minute microbes of typhus multiply in the epithelial cells of the intestinal tract and it is currently assumed that these organisms excreted in the feces of the louse enter the body through abrasions due to scratching. In view of these recent discoveries it can be readily understood why certain writers claimed that typhus may arise *de novo* if the accessory conditions of famine, overcrowding and filth prevail. In such an environment the body louse could thrive and be readily transferred. The absence of a fairly abundant water supply, the scanty use of baths, and other conditions favoring the insect were in operation. Even today the head louse is not an infrequent guest of school children. The rise of cleanliness in the nineteenth century has quite effectually banned typhus. In the World War the disinfection of wearing apparel on a large scale destroyed lice before they could migrate to fresh hosts. Recent studies have indicated that there may be several

varieties of typhus and that one of these is linked to the rat as a reservoir of the virus.

Malaria may be considered a universal disease in tropical and subtropical countries. It has prevailed under a great variety of conditions and is probably responsible for the retarded occupation of the tropics by the white man. The microscope has revealed to the world three types of malaria differentiated by temperature curves and virulence. Laveran was the first to call attention to certain bodies in the red cells. This was in 1881. The mosquito was recognized as intermediate hosts of these same bodies in 1898 by Ross. Before these discoveries a very large literature had already grown up around the external characters and predisposing conditions. It had been discussed from many angles on the basis of epidemics studied and a large body of more or less conflicting evidence on the causes published. Malaria, being a play between three living organisms, a certain species of mosquito, the protozoan parasite, and the human host, would naturally present difficulties to the inquirer who was not aware of two of the factors. These difficulties were accentuated by the complex conditions involved in the life cycle of the mosquito. There were as a consequence many theories presented which fitted certain endemics but not others. Among the hypotheses offered were the following: weather influences, effluvia from marshes, compounds of sulphur and hydrogen, because malaria had been observed near active volcanoes, the excitants and products of decomposition, fungus spores floating in the air, algae of various families, the bacillus of Klebs-Tommasi-Crudeli, and the toxic excretions of living animals and plants. Every one of these theories had its group of active defenders.

It must not be supposed that these theories were based on ignorance either of the clinical disease or the conditions associated with epidemics. It was known that strangers in and

visitors to malarial regions suffered most severely. It was well established that atmospheric moisture and heat were determining factors. High altitude and sandy soil were regarded as inhibitory in degree. The drying-up of wet marshy soil as well as the complete inundation of the soil were both inimical. Operations involving large public works in drainage and the like were known to start epidemics. The partial clearing of virgin soil was favorable to malaria but not through cultivation. Abandonment of once cultivated soil led to outbreaks. The danger to a ship's crew of proximity to a malarial coast was well established. These and other firmly grounded observations are in line with the mosquito. Even those apparently antagonistic may be harmonized with the problems of plankton food for the insect. The mysterious element in this, as in other disease problems, was the very large number of immune or partly immune carriers capable of infecting mosquitoes feeding on their blood and transmitting the infection when on the surface no malaria was in sight. This mysterious phenomenon is linked with the possibility that malaria may appear at any time when the external conditions are favorable. The wide distribution of the malaria-carrying species of mosquito may bring epidemics into northern climates when carriers in the shape of workmen come in to turn up the soil and create stagnant breeding places for the insect. Finally the malaria problem was made more puzzling by the fact that the mosquito is not an obligatory parasite like the louse but predatory in taking its quota of blood in a short time and living free otherwise. This introduced the broad variable factor of the breeding grounds which vary from place to place.

The invasion of certain diseases into territories ordinarily isolated and thereby well protected is illustrated in the medical history of Iceland. Infectious diseases were brought into this island at rather long intervals. They disappeared after a

time and one or more unexposed generations grew up before another epidemic. The island experienced the great epidemic in 1493. In 1644 and 1646, two great epidemics of measles spread over the island. In 1797 and 1827 appeared great scarlet fever epidemics, and in 1825 and 1839 whooping cough was epidemic. An Icelander died abroad in the winter of 1707. In the spring his clothes were brought on shore and among them a chest of linen. A member of the family wore this linen and contracted smallpox. The disease spread over the whole island, thirty-four years after a preceding epidemic; 18,000 out of 52,000 died, among them old persons and lepers. Mostly young persons were attacked. Women had to carry the dead to the church. This epidemic, it will be noted, occurred a century before vaccination was introduced.

This brief statement has barely lifted the cover which the passage of time places over past events. Similar painful recitals of the widespread epidemics of syphilis, of fatal diphtheria and other throat affections, of hospital epidemics of puerperal fever and erysipelas might be given to illustrate the ordeals through which the race has passed. It is generally assumed that history in its preoccupations with wars and dynasties has sadly neglected to record the lives of the populations as a whole and there have been lost many data which might have been valuable to modern medicine in its endeavor to penetrate into the past and interpret the phenomena underlying great epidemics.

During the periods covered by the Middle Ages and up to the nineteenth century plagues among domestic animals were not uncommon. Not infrequently they were regarded as initiating human epidemics. We now know that the larger food-producing animals were not contributory to any of the major human epidemics. Rather the actions of man contributed to the spread of animal diseases. The wars of the Reformation

and the Napoleonic excursions into other countries contributed to a dissemination of the disease in horses, known as glanders, and dangerous to human beings handling them. Strictly cattle plagues were disseminated by armies driving their supply of meat on the hoof. The precise extent of the losses incurred in the food supply of the populations remains unknown. Concerning the causes of the great pestilences the ancient writers looked to the stars and planets and their combinations. Authors in the Dark Ages found the causes in unlooked-for atmospheric and terrestrial phenomena, among them earthquakes, volcanic eruptions, severe storms, the appearance of meteors and comets, and droughts. More recent thinkers and sanitarians looked to the variations in atmospheric moisture and temperature, the rise and fall of the water in subsoil, great fluctuations in temperatures, as favoring causes of epidemics. Today we are inclined to narrow them down to the human and animal world, their intercourse, migrations, the continual fluctuations in habits and modes of life, but especially to the increasing susceptibility of populations during the disease-free periods.

If we go back to the individual plagues as enumerated above, we learn that the four stages of the parasitic cycle were rarely apprehended at the same time. Usually some time elapsed before the elucidation of the cycle was complete enough to offer a convincing explanation of the vagaries of each epidemic disease and a basis for successful procedure against it. In the investigations of the bubonic plague in the 'nineties of the past century, the bacterium was discovered first, then came a knowledge of the rat as a reservoir of the infectious agent, and lastly the rat flea as the transmitter from rat to man. As stated above, in malaria the parasite of the red corpuscle was seen in 1881 by Laveran; the mosquito was pilloried as the transmitter by Ross in 1898.

The Asiatic cholera vibrio was first brought to light by Koch in 1885. Since the cycle of bacterial parasites infesting the digestive tract is relatively simple, this discovery promptly cleared up the disease phenomena. In yellow fever the transmitting agent was demonstrated by Walter Reed and associates to be a species of mosquito. The true nature of the virus thus transmitted was only recently brought to light as an ultramicroscopic organism.

The occurrence of tuberculosis in families led to the view that it was an inherited disease. The demonstration of a characteristic bacterium by Koch in 1882 disposed of this view. The localization of the disease in the lungs or associated lymph nodes in most cases led to acceptance of the simple cycle of expectoration and inhalation. Many other occasional routes are known but the inhalation route predominates and is the only one to maintain a cycle and prevent the disease from dying out. The aberrant routes of the tubercle bacillus led for a time to the hypothesis that it was swallowed and by a circuitous route reached the lungs.

The bacterium of undulant or Malta fever in man was discovered by Bruce in 1887. Not until 1905 was the source of the agent finally determined to be goat's milk. Malta fever was thus a disease of goats. In man it cannot survive because of the absence of a satisfactory cycle. If perchance it should be capable of multiplying abundantly in the digestive tract or the urine, it might also become a human disease like typhoid fever.

It would be unfair to the generations of scientists who lived before the present half-century of intensive development of parasitic cycles not to mention the large amount of accurate knowledge brought together by them on all parasites visible to the unaided eye and with low powers of the microscope. The recent accelerated progress is largely due to the improve-

ments in the microscope as well as to advances in the natural sciences of biology and chemistry and physics.

Respiratory diseases of an infectious character due to the invasion of the mucous membrane of throat, tonsils, and nasal passages have in a sense remained refractory to a complete understanding chiefly of the underlying microbic causes. The cycle itself can be conceived as simple enough, the direct inhalation of fresh spray from mouth and nose and of the dried spray in dust. To these may be added contacts of various types with the secretions in unsterilized eating utensils, towels, etc. During the great pandemic of influenza in 1889-1890 a minute bacillus was discovered in the sputum which came to be known as Pfeiffer's bacillus. It was later found in all parts of the world where genuine influenza prevailed, but not regularly. The frequent disappointments led to a division in the ranks of investigators, one claiming the Pfeiffer bacillus to be the true cause of epidemic influenza, the other that it was merely a concomitant or satellite of the true cause. Very recently certain discoveries were made which may bring the two opposing parties together. In the study of an influenza of swine, Shope and Lewis found both a well defined bacillus of the Pfeiffer type and a virus not visible or cultivable. The two together produce the swine influenza. About this time Dochez, in the study of common colds, also brought to light an invisible filtrable agent. These discoveries make probable in the near future a demonstration of human epidemic influenza as a double infection. The fluctuating virulence of such epidemics may depend on the virulence of the associated bacterium or on that of the invisible virus. In other words, we may have two independent variables working together to determine the fate of large populations.

This cooperation of two or more organisms in the modification and perpetuation of diseases is likely to play an increas-

ingly formidable part in the future fate of human and animal life. These agents may be transmitted together from any diseased individual, or one may be present as a chronic parasite of the mucous membranes, ready to reenforce the new invader. These combinations are not new to medicine. Smallpox in its advanced stages of suppuration is associated with the common pus cocci. Deaths are not infrequently due to the secondary invasion of streptococci. All mucous membrane affections are subject to bacterial complications. Distemper in dogs, due to an ultravisible virus, is frequently prolonged and aggravated by a bacillus which parasitizes the respiratory mucous membrane. In the disease of turkeys popularly known as blackhead, the protozoan parasite which destroys the walls of the ceca and secondarily the liver may be started by feeding eggs of a minute worm which lives in the ceca of chickens and turkeys.

The practical application of discoveries of medical science together with its associates, the natural sciences, and its influence on the rise and decline of parasitic diseases will be discussed farther on. An attempt to bring together the biological causes of the wave motion of epidemic diseases involves two categories, the appearance of epidemics of existing diseases and the birth of new diseases.

The ultimate cause of fluctuations in the intensity of diseases is, as stated above, either a variation in host resistance or in the virulence of the parasite or of both together. Whatever influences these, has some determining influence on the host-parasite conflict. The main problem then consists in tracing the factors which modify host resistance on the one hand and parasite virulence or invasiveness on the other. Host resistance may be affected by a rise or fall of acquired immunological characters such as are gained in passing through a disease or lost in its absence. It may be due to spontaneous genetic varia-

tions in a given population in which the highly susceptible perish and leave the field to the other groups. In recent years selective breeding of mice, guinea pigs, rabbits, and poultry has brought to the surface naturally resistant as well as naturally susceptible families in which preliminary exposure to the experimental disease had been rigidly excluded. The inbreeding had not established a complete immunity or susceptibility since a certain per cent of one group failed to survive and a certain per cent of the other to die following administration of the bacteria. The inference can be drawn that the resistance is quantitative and that a new protective mechanism is not developed. Webster has recently shown in experiments on mice that resistance to one disease developed by selective inbreeding is associated with resistance to certain other bacterial diseases. This protection against a group of disease is not general, however, since exceptions appeared. These recent developments are in harmony with observations made during all epidemics that certain individuals remain well, certain ones die, and certain others become ill but recover. No light is thrown on the inner processes by these results but they tend to stimulate anew the study of resistance and susceptibility. The changes in the parasite may be referred to various factors. The influence of a resistant host has been mentioned, also the cooperation of two parasites in colds and influenza. The ultramicroscopic agent is associated with some bacterium. That there might be an antagonism between certain resident bacteria in the mucous membranes and the incoming epidemic agent is not to be gainsaid. The proof, however, is difficult.

The forces making for disease have been greatly assisted by the expanding activities of the human race since the discovery of new continents and contact with hitherto shut-in, segregated communities of human beings and animals. The

present-day speed of transportation will carry any disease however short-lived over the entire globe. The bringing together of hosts and parasites of every description sooner or later tests thoroughly the capacity of the new host and parasite to get on together and develop a new disease. When some apparently new disease appears we are confronted with the question whether it is not some old type in a modified guise or some animal disease the virus of which has undergone specific modification. The question, whose answer is of such significance, is specially refractory to investigation when the infectious agent is a virus or ultramicroscopic form. It is highly doubtful that new diseases or host-parasite combinations are in progress of development from saprophytic or free-living forms. More probable is the modification of existing parasites through aberrant parasitism in alien hosts or the advance of superficial, mucous-membrane forms into invasive types.

The decline and disappearance of once widely prevalent diseases is no less impressive a fact than their epidemic rise. Europe has witnessed the decline of leprosy and its disappearance from all but a fringe of the continent. Tuberculosis has been steadily declining in mortality for more than a half-century. These are strictly endemic diseases without a break in continuity and this endemicity is a function of the peculiar character of the bacteria. The decline of these diseases is closely interwoven with social changes to be touched upon in the last chapter.

We have seen that the invasion of territories after a long absence of the infecting agent brings epidemic forms of the resulting disease. The inhabitants have lost something that protects those among which the parasite has prevailed. The invasion of wholly fresh populations is scarcely possible today owing to world-wide intercourse. It is highly probable that

the continued prevalence of a disease in a nearly closed or isolated population tends to raise the virulence of the parasite to meet the rising host resistance of that population. When the same parasite is carried to other populations this rise in virulence must be added to the loss of host resistance in starting an epidemic.

The brief statements concerning some of the world scourges brings into clear relief the great importance of a complete knowledge of the fourth phase of the parasite cycle, that one which has to do with the transit of the parasite to fresh hosts. The groping of men for some understanding of the apparently contradictory behavior of epidemics, the tomes written to support some now outworn theory are witnesses of the mental labor expended, not uselessly perhaps, but nearly so. The only benefit to be seen was the training of the investigators and the renewed desire to continue the attack until the data should begin to fall in line and meet general acquiescence. Next in importance to the discovery of this fourth stage is the putting in action means to suppress it. The suppression cannot rest for none of the plagues have been extinguished. Should misfortune bring back certain conditions these plagues would reappear from some remote or near corner where they are slumbering in a resistant population. The final suppression presupposes a world organization of human society without wars, and disarmed, such as the most pronounced idealist of today can scarcely conceive, but towards which human society must tend to survive in the struggle with animal and plant life, microscopic and ultramicroscopic.

IX

THE UTILIZATION OF DISCOVERIES IN PARASITISM

THE objectives of research as a mere accumulation of data or the display and parading of acquired knowledge in a world otherwise in motion is outmoded. Penetration into mysteries may thrill the penetrator and occasionally others, yet this is not enough. Discoveries and inventions must be made to yield some contribution towards that rather vague goal, the welfare of mankind. More specifically the study of parasitism and disease appeals to the human desire to live and be free from disease and it is this strong urge that furnishes ample stimulus to the altruist as well as to the charlatan. Parasitism is greatly favored by large numbers of individuals insofar as they offer the best opportunities for new parasites through trial and error methods to arise or for existing ones to develop a more complete adaptation. Large numbers of hosts furnish the starting points of epidemics and nature reduces the superabundance of wild life through disease. Nature may be said to abhor a crowd.

In view of this obvious tendency in nature, the dominance of the human race is in conflict with it. It is this conflict which stimulates research into natural law and the means to meet its requirements as well as to circumvent them. To submit to and to circumvent nature are practices cultivated side by side. We cannot return to nature as defined by animal and plant life, for such a course would destroy civilization. We cannot fly in the face of nature continually for this practice would lead to heavier burdens and eventually to catastrophe. An

eclectic course steering carefully as we go along to avoid the visible dangers seems to be the proper choice. The human race is in a rather delicate, unstable relation to its environment. Its course is frequently left to chance, in the hands of incompetents instead of being guided by the cooperation of those best equipped. Only now and then is the voice of reason heard in the rare intervals when the human din subsides long enough for the race to catch its breath. The value of human life is profoundly distorted and the untiring labor devoted to attempts to save a single life is daily and hourly flouted on our highways. Important devices to protect community health such as vaccination against smallpox are set aside because the accidental individual death rate resulting from their application may be in the second or third decimal place of a per cent. Great expense is incurred and heavy burdens placed on the community to protect the supply of water and milk, when the neglect of some of these precautionary measures would hardly approach the toll of deaths by accident. It is in an atmosphere of this sinister composition that research to find ever more thorough and simpler methods for protecting life and health is going on. Even in pursuits less serious than those which lead to destruction of life we are actively carrying on the very habits, customs, and operations against which medical science is continuously endeavoring to discover remedies or preventives. Notwithstanding these countercurrents, science is steadily deepening its insight into nature's laws and guided by this insight controlling the daily and hourly conflict of nature with mankind. In these conflicts control of disease is only one of the many fronts maintained by science. The self-protection of the individual, "rugged individualism," the first to suggest itself, becomes more and more restricted with the growth and density of population. His freedom of action is slowly narrowed down to conform with the social

law. His protection from certain diseases is delegated to the social organism. Hence the development of a public health machinery. There are, however, certain residual practices in which his freedom of choice has still some play. Before discussing these, let us see what procedures are at our disposal in meeting certain diseases. They may be stated as follows: (1) The care and strengthening of the normal defenses of the body. (2) The raising of the specific defenses by the use of vaccines and serums. (3) The suppression and destruction of parasites in transit by a study of their entry into and exit from the body and the vehicles of transmission. (4) The use of specific curative substances during disease. These are chiefly antitoxins developed to a high degree of potency in certain large animals. (5) The use of synthetic specifics such as quinine in malaria, tryparsamide in sleeping sickness, arsphenamine in syphilis.

Viewing the problem from another angle we might divide the responsibility for suppressing one or the other phase of the parasite cycle as follows: (1) The phase of entry of parasites must be fought by the individual or those in his immediate environment. (2) The suppression of multiplication in the body belongs to the domain of medical practice. (3) The control of the exit of infectious agents belongs to the affected individual and to medical practice, hospitals and sanatoria. (4) To control the transit from host to host is eminently the task of public health and sanitary science.

The importance of what we may call the first line of personal defenses is such as to merit some detailed statement. These defenses are in part anatomical or structural, in part physiological. They are possessed by all living beings, and are developed in relation to the medium in which the individual lives, the climate, and social habits and customs. They are chiefly external defenses to protect the delicate internal

mechanisms from invasion and injury. They are adapted to neutralize blows, to intercept the passage of pointed objects, to protect against heat and cold and chemical irritants, to maintain a uniform internal climate of the body, and to prevent the invasion of microorganisms. Among these non-specific defenses two tissues stand out preeminent, the integumentary covering or skin and the mucous membranes which line all the cavities that stand in direct or indirect communication with the exterior.

The structure of the skin is admirably adapted to prevent the entry of microorganisms or their multiplication. It consists of a deep and a superficial layer. Each of these is subdivided into strata of slightly different character. We are interested chiefly in the superficial layer or epidermis. This consists wholly of cells differing from within out in appearance and function. The deepest layer consists of cylindrical cells which rest upon the inner tough and fibrous layer of the skin. On these rests a layer or stratum of roundish cells. These two make up the soft layer of the epidermis and they in turn are covered by the outer layer, which consists of flattened cells forming a very compact layer. These cells become flattened and horny near the surface, wear away gradually and are replaced by cells from below. It should be stated here that all the cells of the epidermis are derived from the lowest layer of cells by a process of division. Each cell grows large and divides into two daughter cells. These in turn go through the same process. The new cells are slowly pushed upward as the outer layer wears away, those next below take their shape, habit and position, to be in turn cast off and replaced by a fresher generation from beneath. It is this layer, the cuticle, which is the only barrier that stands between us and certain highly infectious disease germs. It is adapted to act as a barrier for it carries no vessels whatever. Hence a slight superficial abrasion

would not expose and injure any vessels which might carry into the body certain microorganisms. If, however, this cuticle is completely removed, lacerated or cut so that oozing or bleeding occurs, certain bacteria might enter and produce severe fatal disease. Fortunately for us this class of bacteria is uncommon.

One of them is the bacillus of bubonic plague. Now and then a surgeon succumbs to the bacteria of certain septic diseases requiring surgical intervention because the bacteria entered through a small cut or abrasion of his hand or arm. From these dangerous frequently fatal diseases there range all gradations of infectious skin diseases, to the mildest, short-lived pimple.

The cavities of the body communicating with the exterior, such as the digestive and respiratory tracts, are likewise exposed to injury of various kinds and they are protected each in a special way against definite dangers. The digestive tract is occupied with many different functions throughout its course and its lining membrane varies accordingly from place to place. The necessity of balancing between functional efficiency and protection against injury has led to the evolution of a unique lining. Throughout, the membrane is covered with cells differing in form and structure according to the special work to be done. In the upper portions used merely for the passage of foods the cells are arranged in layers somewhat like those of the skin. In the stomach and intestines where the mucous membrane both secretes digestive fluids and absorbs digested products, the membrane consists of a single layer or pavement of tall cylindrical cells, situated close together. Whenever a cell becomes worn out or injured a new one is formed to take its place. This delicate cellular covering is all that stands between an active bacterial flora in the digestive tube and the bacteria-free interior of the body. Among

the lower animals whose food is uncooked and frequently in an active stage of bacterial decomposition, the myriads of bacteria consumed pass through the intestines without breaking through this delicate barrier. These cells select the right food with unerring certainty and pass it on through themselves into the lymph and blood stream behind them.

Under certain conditions when such bacteria as those of typhoid and tuberculosis pass through the intestinal tube in food and water some penetrate the wall and set up disease. How they succeed is not definitely known. Either they enter at points where the epithelium has been accidentally abraded or else they possess special powers in virtue of which they cause death of the surface epithelium, or they secure admission through the intact membrane which is denied other species. Much attention has been bestowed on this subject but it presents peculiar difficulties and no satisfactory information is at hand. Experiment has shown that young animals are more easily infected by way of the digestive tract than adults. The mixing of certain bacteria with the food will infect young calves and colts when the same repast will have no effect whatever on adult cows and horses. This harmonizes well with the general opinion of medical science and practice that infants are more easily infected through the digestive tract than adults. Public health has become fully cognizant of the importance of clean food for infants, and physicians to the importance of a clean environment owing to the infant's habit of identifying objects by their taste. The possibilities of infection through a mouth lined with defective teeth is commanding much attention at present. The tonsils are frequently accused of permitting bacteria to enter through them. It is safe to assume that wherever defects exist in the protective covering they will be discovered and made use of by unwelcome bacterial guests which happen to enter the mouth.

Besides the bacteria which must penetrate the mucous membrane before they can multiply and incite disease, there are others which multiply in the digestive tract and through their activities injure and destroy the cellular covering.

The respiratory passages contest with the digestive tract the chief place as portals of entry for disease germs. Yet they also are admirably protected against invasion. In the nose, the peculiar configuration and shape of the cavities cause fine particles in the inspired air to adhere to the mucous membrane. Beyond this and extending into the finest ramifications of the air tubes, the mucous membrane is covered with cylindrical cells of peculiar character. The surface of these cells is beset with myriads of excessively minute hairlike bodies, called cilia, which are in continual motion, like a whip held at one end. The wave movement is outwards towards the mouth and serves to propel back any particles which escaped through the nose and which the inspired air deposited on them. Yet not all dust is kept back in this way. In human beings carrying on occupations in dust-laden air the lungs themselves gradually become the depositary of much material which escaped both nose and ciliated epithelium. The miner's lungs become sooty black. In animals exposed to dust, some particles of soot and quartz stop in the lungs, others pass through them into structures behind the lungs, the so-called lymph nodes, where they are finally deposited. The evolution of animal life went on in a dust-free atmosphere, for except in certain deserts dust is an invention of man, and the provision for disposing of dust once in the body is inadequate. If particles of dust can escape the protective agencies of nose, throat, and air tubes, and finally land in the depths of the lungs, the same can take place with tubercle bacilli. It is generally supposed that the germs of smallpox,

measles, chickenpox, and other eruptive diseases enter the body somewhere in the respiratory tract.

The portals of entry for disease germs comprising the skin and contiguous membranes, the digestive tract and the respiratory tract are very well guarded by nature and the infectious agents which actually succeed are probably a small fraction of those warded off automatically by the various protective devices. It is obvious that these devices are limited in efficiency by the nature of the functions the tissues must perform. Our skin might be much thicker and firmer to protect us but it could hardly be the delicate temperature regulator it now is. The lungs must have a definite regular supply of air and any even slight obstruction in the passages makes for discomfort and debility. The mucous membrane of the intestinal tract must give free passage to the digested foods and any obstruction to the ready absorption of fluids leads to various derangements at once. These delicate barriers must therefore be kept in normal condition as far as possible by a careful adherence to the rules formulated by hygiene for the care of the skin, of the mouth, for the proper selection and mastication of foods, and the proper use of the respiratory muscles in breathing. Whatever tends to keep these functions in perfect condition reduces greatly the chances for infection after exposure.

The perfect functioning of the body is not in many directions sufficient to prevent the invasion of pathogenic organisms. We have noted the partial protection of individuals towards endemic diseases, such as have prevailed locally over long periods of time, and the gradual pushing back of infectious diseases towards the young which in turn are partly protected through intrauterine transfer of protective antibodies. The young and older individuals acquire a heightened resistance towards the actual outbreak of disease by taking in

minute doses of the infectious agents. The resistance thus established is not infrequently broken down in tuberculosis by unhygienic living, severe strain, by exposures, traumatism, excesses. We have furthermore seen that in all species certain individuals and families have a high resistance which is genetic in origin. To eliminate the uncertainties, since natural and acquired resistance are not open to preliminary tests and no one knows just where he stands, there has been developed towards certain diseases a method of artificially raising specific resistance with the help of so-called vaccines. They differ among themselves and have been found applicable to only a few diseases thus far. There is, however, no *a priori* reason for thinking that vaccines may not be discovered for more diseases in the future. Vaccines act essentially to produce a mild attack of the disease to be guarded against. They imitate nature. The mild attack is, however, so slight that it usually passes with but a trace of fever. Why such slight impacts should ward off the calamities of an open attack is explained by the nature of infectious disease. The momentum of the parasite increases as it enters the body until checked by the countering activities of the host. This is well shown in the administration of antitoxin which is the more effective the earlier it is administered. If before the infection, it may prevent the attack entirely. If given late in the disease, it may fail entirely. In this stage the host itself may have developed its own antitoxin or have become submerged by the toxin. Vaccines act similarly in giving the system the initial resistance which enables it promptly to check multiplication at the site of entry of the parasite.

The development of preventive inoculation and vaccination forms a most interesting chapter in the history of disease from which a few salient facts will illustrate our theme. Vaccination came as a result of everyday experience with infectious

diseases at a time when nature could perform the most momentous experiments upon man with little or no resistance on his part, except what superstition at times called forth. In these great social crises, physicians had ample opportunity to discover by simple observation two principles upon which vaccination is grounded. In any group of individuals passing through an epidemic disease, we may discern a number of sub-groups according to their behavior. A few die very early, some at a later date, a certain number become ill and recover, and a residuum do not become ill at all. The relative number belonging to each group will vary with the virulence of the disease. Those that have been sick and have recovered do not as a rule suffer from the same disease a second time. Those that have been exposed but not sick also do not contract the disease later if exposed to it again.

These two facts, characteristic of nearly all infectious diseases, form the groundwork of preventive and curative vaccination. They suggest the possibility that by some means we might either prevent the occurrence of disease altogether, or else change it from an otherwise severe to a light, or from a fatal to a non-fatal affection. Attempts to protect human and animal life by applying the two principles quoted were made in the earliest times of which records are preserved. In times of epizootics, domestic animals have been exposed by their owners to the milder infections so as to hurry along the disease. They have also been inoculated directly with the virus of dangerous diseases with the hope that the disease thus produced would not be so fatal as the spontaneous attack. Similarly, children have been exposed intentionally to mild types of the eruptive diseases, with the expectation that if they contracted the mild disease, they would be protected against later, perhaps more fatal, epidemics. The most important application of the principle of inducing a mild attack against a severe

or even fatal one is inoculation and vaccination against smallpox. There is perhaps no disease next to leprosy so loathsome as this, none which has played so important a part in human life everywhere in the world. History tells us that smallpox existed thousands of years ago in China and India. The earliest records of its appearance in Europe date from the sixth century. It was generally recognized in England early in the sixteenth century, and introduced about the same time into America by the Spaniards. It was widely disseminated in the eighteenth century, and became an appalling social evil. About every tenth death was due to smallpox, and the mortality was 30 per cent or more towards the end of the century. It is estimated that 60,000,000 perished during the eighteenth century, 30,000 per year, in France. It attacked all classes and threatened the existence of royal families. Among the victims of smallpox may be mentioned William II of Orange, Emperor Joseph I of Germany, Louis XV of France, two children of Charles I of England, a son of James II, his daughter, Queen Mary, and his grandson, Duke of Gloucester, two German emperors, six Austrian archdukes and duchesses. Empress Maria Theresa of Austria nearly succumbed to it at an advanced age. Its prevalence gave rise to the dictum that few escape pox. Its victims were chiefly children. Since all must have smallpox, according to the experience of the age, many exposed themselves voluntarily in mild epidemics.

In the East a method of combating the disease had arisen which consisted in the direct inoculation of smallpox virus into the skin. In the spontaneous disease the virus is probably inhaled. The introduction of the virus by way of the skin modified the disease enough to reduce greatly the mortality and resulting disfigurement. In 1721 this method was brought to England from Constantinople by Lady Mary Montague,

who had one daughter inoculated. Up to 1728, 897 had been inoculated with a total mortality of 17. The method found many adherents. Inoculation hospitals sprang up and people went to these to be inoculated and pass through the disease. It spread to this country, and was championed by Dr. Zabdiel Boylston of Boston. As frequently happens under such conditions, he brought down on him the fury of the mob and came near losing his life. On the other hand, smallpox parties were formed among the upper classes by going to some hospital and having the inoculation disease together. There can be no doubt that inoculation greatly reduced the mortality, and protected the inoculated from future attacks. It was not without its risks, however, either of disfigurement or death. Being the genuine disease, it tended to maintain and even disseminate the infection.

The destructive tide of smallpox was turned by Edward Jenner at the opening of the nineteenth century. He observed in his practice that an eruption on the udder of cows called cowpox or kinepox tended to appear on the hands of milkmaids and that they were resistant to smallpox. This observation led to the use of cowpox in the preventive inoculation or vaccination—as it was subsequently called—against smallpox. Following the introduction of this vaccine, cowpox was intensively studied and the inference drawn that it is smallpox rubbed into the teats of the cow by a person affected with mild smallpox but profoundly altered and mitigated by the system of the cow so that it could no longer produce smallpox in man. It should be stated that this change from smallpox to cowpox does not follow any and every inoculation of smallpox into the cow. In fact the transformation is extremely rare, so that controversies arose as to the precise origin of cowpox. Several investigators, however, did produce a mutation of smallpox virus in the cow after many failures. Other domestic

animals have their pox. Sheep, swine, and horses have been afflicted. Modern sanitation soon disposes of these diseases, however. Jenner thought that cowpox was derived from horsepox or grease. During the World War a Dutch investigator discovered an outbreak of horsepox, which he passed on to cows where typical cowpox appeared.

Following Jenner's work at some distance, Pasteur's investigations, which cover the later third of the nineteenth century, have been of fundamental importance in the extension of vaccination to other infectious diseases. He took as his chief problem the mitigation or attenuation of the microorganisms of different diseases, so that inoculation would produce only a very mild, scarcely recognizable, disturbance, and yet afford protection against the same diseases.

Taking events in chronological order, we find Pasteur first engaged in studying chicken cholera and its microbe. This organism belongs to the group of septic bacteria which after entry into the body spread rapidly into all parts, and promptly destroy the victim. It is a close relative of the bacterium of bubonic plague. Injecting cultures of this organism which had stood for some time unrenewed, he found to his surprise that the fowls recovered after a short illness. Inoculated again, with fresh virus, they resisted. Here was a vista of unending usefulness opened up to him in combating the microbic plagues of man and animals, for the proper understanding of which he fought so valiantly in the work on fermentation. The possibility of attenuating the virulence of microbes and using them as vaccines became thereafter the leading motive of his active life. The attenuation of the chicken cholera microbe he referred to the oxygen of the air as cause. This was, as we now know, but a partial explanation. The bacteria of this group quickly perish in our culture media, and immunity can be produced by injecting bacteria killed by heat. His results were due in

part to dead, in part to dying, bacteria equivalent in their action to dead bacteria. It may be stated here that cultures attenuated by age have been rarely used as vaccines on account of the uncertainty of the virulence.

Surmising that since bacteria differed from one another a method of attenuation suitable for one bacterium would probably fail if applied to other bacteria, Pasteur soon displayed his originality when he began to devise means to protect his country against the yearly ravages of anthrax. The bacillus of anthrax as a biological entity stands far apart from the microbe of chicken cholera. Here the difficulty entered in the form of a highly resistant spore. This difficulty was overcome by cultivating the bacillus in chicken broth kept at a temperature of 41°-42° C., which still permitted the bacilli to multiply, but interfered with the formation of spores. At this temperature the bacilli became slowly weakened in virulence. By grading the time during which the bacilli are cultivated at this high temperature, strains of different degrees of virulence may be obtained. Perhaps the strangest outcome of this discovery is the fact that this diminished virulence persists, i.e., it is transmitted to other generations. The dysgenetic temperature is not needed after the attenuation has been effected. The change, once produced, remains. At the same time he demonstrates again a principle which had been developed some years before—that the bacillus thus attenuated by heat may be brought back to its original virulence by inoculating it into a series of susceptible animals. This return to virulence is the counterpart of attenuation or reduction in virulence.

The modification of bacteria in cultures by heat formed the foundation of methods used by others, in which various substances, such as alcohol, carbolic acid and formalin are employed to reduce or extinguish virulence. A few years later Pasteur was attracted to another infectious disease of animal

life, which, though not dangerous to man, was causing great losses in France. It was an infectious disease of swine. In attempting to find a method of producing a vaccine he inoculated the original virus into a series of small animals, and thereby modified it into a vaccine. This method, which in the case of swine fever did not prove of much value, led later to perhaps the best of Pasteur's efforts to save human life, his method of vaccination against rabies.

Some years ago the principle underlying this method was applied by Koch and Behring in the vaccination of cattle against tuberculosis. The tubercle bacillus as it is found in the most frequent type of the human disease, pulmonary tuberculosis, does not produce tuberculosis in cattle, even when injected directly into the blood. This is perhaps the severest test which can be applied. The injection raises very decidedly the immunity of these animals, so that they will hold out against a dose of the bovine tubercle bacillus which will surely kill an untreated animal. In this instance, nature has evolved two races of bacilli coming from some common ancestor. One race was produced by passages through man; the other by passages through cattle. The end products differ from one another. The use of the human type of tubercle bacillus as a vaccine for cattle has been abandoned at least for the time being.

Perhaps the most beneficent and spectacular of Pasteur's work is the development of a vaccine against rabies. Following the principle used in his studies of rouget in swine, he modified the rabies virus of dogs by inoculating rabbits in series, until at the end of a long series the virus was so mitigated that it had little if any effect on man. To reduce any untoward effects to the utmost, this vaccine was injected at first following prolonged drying which killed the vaccine. After repeated injections of the dead vaccine, living vaccine

completes the treatment. This vaccination differs from all others in that it is only applied to those actually exposed to the disease through bites from rabid animals. The vaccine reaches the vital centers first and neutralizes the virus.

The simplest method of producing immunity is the injection of the infectious agents which have been killed by heat or some chemical agent. This procedure has established itself for protection against typhoid fever and is reported as efficient against Asiatic cholera. It is, however, not generally applicable, either because the immunity sought for is not developed, or the culture too toxic, or the infectious agent not cultivable. When applicable the method may permit the injection of several different vaccines in the form of heat-killed cultures mixed together. The success of heat-killed vaccines supports the assumption that the suppression of infectious agents at the portal of entry is comparatively easy. Otherwise it would be difficult to understand how the body can be protected simultaneously by four different vaccines mixed together, such as those used by Castellani in Serbia during the war. This so-called tetravaccine contained typhoid bacilli, paratyphoid bacilli A and B, and cholera spirilla. The appearance of agglutinins was regarded as indicative of immunity.

A vaccine against tuberculosis which has received much attention in recent years was introduced by Calmette of the Pasteur Institute. The universality of this disease and its tenacious prevalence gives any vaccine a certain status. Calmette's vaccine consists of living bovine tubercle bacilli cultured over a long period of time on a special substrate of potato plus bile. These bacilli have lost enough of their virulence to make injection a local harmless affair. Although used in many localities for some years a final judgment of the value of this vaccine cannot yet be rendered since statistics of human diseases

are beset with many disturbing factors which can only be smoothed out by large numbers. The persistence of tubercle bacilli in the body is such that a complete recovery may be simulated for a time but exposure and strains of various kinds may bring about a renewed multiplication of the bacilli. Observation of individuals treated very early in life must be continued well through adolescence to be of any real value.

The public has also become acquainted with efforts to prevent diphtheria with the use of a balanced mixture of diphtheria toxin, a bacteria-free filtrate of the fluid in which diphtheria bacilli have multiplied for some days, with antitoxic blood serum prepared in the horse by injections of toxin. The mixture is harmless although containing relatively a large amount of toxin, because controlled by the antitoxin. In the body the former is slowly given off to produce a strong active immunity. More recently it has been shown by Ramon of the Pasteur Institute that the toxin alone can be used if detoxicated by treatment with formalin. The resulting product is known as anatoxin.

The extensive researches on yellow fever conducted under the auspices of the Rockefeller Foundation and by workers under French, English, and South American direction have shown the necessity for protecting all those engaged in handling the virus, for up to the year 1932 five scientists had lost their lives among thirty-two passing through the disease contracted in laboratories. The most promising method developed thus far is a combination and modification of older methods. It was found that when the virus was injected into the brain of mice in series, similar to the Pasteur method for reducing the virulence of rabies by passage in series through rabbits, it became modified and of far less pathogenic power for monkeys. Immunity in human beings could be developed either by injecting this modified virus and an immune serum

separately or by injecting a mixture of dried virus and dried serum stored and redissolved when needed for vaccination. It is to be hoped that the danger of contracting yellow fever by foreigners in countries where the disease is endemic may be entirely removed or its fatality prevented. It is obvious from the foregoing that each disease demands its own vaccine which must protect while it does no harm. It is the latter requirement which has limited the application of vaccines. For animals life has only economic value and methods of protective inoculation are in use which might lead to serious accidents in man. Thus one form of inoculation now in use for rinderpest, hog cholera, and dog distemper is the injection of a highly potent serum on one side of the body and a carefully adjusted dose of the actual virus on the other side.

Vaccination has certain defects when applied towards diseases of chronic character. The heightened protection may prevent a fatal outcome but not a milder form of the disease. The vaccinated individual may then become a carrier. This difficulty has been in evidence in certain animal plagues. When ample means are available, infected and diseased livestock is killed. This radical procedure demands highly accurate means of diagnosis in the living animal to prevent unnecessary slaughter. That vaccination by itself does not suffice to eliminate certain diseases has been duly recognized and since the beginnings of scientific microbiology the efforts of medical science and practice have been to supplement vaccination and make it in certain diseases unnecessary. This brings us to the most important phase of private and public health activity—the suppression of parasites in the fourth stage of the cycle in their passage from host to host. Public health activities are engineering activities deriving information and rules of procedure from the laboratory, primarily the bacteriological, supported and reenforced by the medical

clinic as well as by all natural sciences in varying degree. Public health administration derives its authority from the fact that the individual living in groups is quite unable to protect himself single-handed against the various streams and currents of infection proceeding from other members of the group or community. The higher social unit must take a hand and formulate the rules for the behavior of those shedding infectious material. It must also close to the various viruses and parasites their avenues of normal intercourse. To do this effectively and without partial paralysis of everyday life it became necessary to study all infectious agents, not only in transit but also as they leave the sick and enter the well body.

It is difficult to draw a line between individual and mass protection. They shade gradually one into another. As individuals we tend to build an aseptic zone about us at home and abroad. In the home we are more or less masters of the situation since we can sterilize and pasteurize at will. There are, however, minor breaks even in the home, too numerous to mention. As soon as we leave the home this aseptic zone is under control of public agencies. The common drinking cup and towel, the dishes in restaurants, the numerous physical contacts with outdoor objects in public halls, conveyances and the like, all point to the helplessness of the individual and the necessity of group protection by means of a sanitary code of rules and regulations to control the indiscriminate transfer of infectious agents and to bind the individual to do his share in preserving the public health.

Each parasite has its own mode of transmission and the measures to be applied differ accordingly. To describe them in detail would be equivalent to reciting the history of modern microbiology. The citizen should, however, know something of the problems to be met, for he pays for public health

activities, which like other social activities are costly and may go politically astray. For the diseases due to parasites of the digestive tract highly expensive plants for water supply and sewerage have been established. The problem of sewage remains unsolved as long as our streams and partly closed bays receive unfiltered sewage, garbage, and other germ-laden cast-off material. Food inspection has become a routine task of federal and local governments. To protect the public from diseased meat and decayed milk, inspection of various kinds has been in operation for some years. The common house fly has been reduced in numbers and even completely driven out in spots by concerted action of public and private agencies.

The transit of infection through the air has been a more difficult problem and as yet partly uncontrolled. The crowding of passengers in public conveyances, halls, and thoroughfares gives the respiratory diseases a favorable opportunity to spread. On the other hand, expectoration in public places, an almost universal habit fifty years ago, has been pretty effectually suppressed by concerted and continued effort. This campaign has been greatly aided on the one hand by disseminating information concerning tuberculosis and on the other by the hospitalization of patients with open tuberculosis. In general adequate ventilation of buildings in which large numbers of people gather at intervals and proper ventilation of schools may be considered a necessary procedure to keep down respiratory diseases. The suppression of insects and arachnids which transmit various parasitic diseases is also a public problem requiring for its solution a thorough knowledge of the life cycle of the insect itself.

We have seen that in certain diseases, to mention only diphtheria, typhoid fever, and malaria, the parasites may be present in the system for some time after recovery. Such carriers form a serious problem. To intern carriers for indefinite

periods seems inhuman. Instruction of the victims to the potential dangers of their person to their surroundings and how to minimize such dangers until the system is free from infection seems to be the most reasonable procedure provided such persons remain under public health supervision and their environment is closely scanned for possible untoward effects. The determination of the continuing infectiousness of such carriers by laboratory procedures has been given much attention and ingenious methods have been devised both to find the hold-over parasites and to determine their capacity to produce disease.

Besides the attention given to prevent sick and recovered carriers from endangering others and to safeguard all kinds of food from acting as vehicles, much attention has been bestowed on destroying infection in the inanimate surroundings of the sick, the rooms occupied, the bedding and furniture. The tendency today is to place less emphasis on these objects and concentrate on the carriers themselves. Tracing infectious agents in the immediate surroundings of the sick is a difficult and, for many infectious agents, a futile problem owing to the impossibility of detecting them. Only specially favorable conditions make success possible. Such conditions were at hand for the tubercle bacillus. Soon after the discovery of this bacillus Cornet made painstaking experiments to trace these bacilli about patients afflicted with the open disease and practising various habits tending to scatter the bacilli. His results showed that while bacilli may be demonstrated in dust near the patient's bed, they become scarce as the distance from the bed grows. In the streets they were not found. These experiments do not claim complete accuracy owing to the experimental difficulties, and in view of the widespread tuberculin sensitiveness of human beings in cities it is safe to assume that

the human body is a better test for the presence of tubercle bacilli than any method that can be put into practice.

Public health measures are directed chiefly against bacteria and other infectious agents assumed to exist somewhere in our midst at all times. These measures are in continual operation and any neglect has in the past proved dangerous and almost catastrophic in certain communities. When certain infectious diseases break away from endemic foci, usually from the Near and Far East, and meet unprotected, non-immune countries, epidemics and pandemics result. Such diseases demand not only the stricter practices mentioned above but they may demand special measures fitted to the parasite involved. As illustrations two epidemic diseases may be mentioned. As protection against Asiatic cholera in the period before the discovery of the vibrio and its cycle, military cordons were formed to prevent both exit and entry into the infected country. Since that time new, more humane ways and means of preventing spread have been found. Individuals, especially men engaged on rivers in boats, rafts, and the like, become the center of diagnostic procedures. The stools of all suspects are examined for the cholera vibrio and carriers are segregated until the stools are found free. In addition to the permanent laboratories, temporary field laboratories are set up to meet the unusual demands for the bacteriological examination of excreta. The bubonic plague is a different phenomenon and the cycle of the bacterium through the rat and the rat flea focuses all measures on rats in ships coming from infected ports. Likewise within the infected territory every measure which promises the destruction of rats is put into operation. All rats caught are examined bacteriologically to trace infection and locate the foci of the rat disease which must coincide sooner or later with cases of human plague. The pneumonic form of human plague, due to a more viru-

lent and slightly modified race of the infecting bacterium, naturally requires additional measures to segregate the sick, since direct transmission becomes the rule.

The infectious and parasitic diseases of the valuable domestic animals are fortunately not prevalent everywhere but scattered in foci throughout the world. Some are tied to the soil, others to insect carriers, still others are independent of such controlling factors and may thrive anywhere. To prevent the introduction of such diseases into countries free from them, quarantine is imposed before free entry, the length of which is gauged by the character of the disease and the associated microbe. Several foreign plagues which had gained a foothold in the United States were exterminated by a destruction of all diseased and exposed animals. Similar procedures have made possible the complete extermination of rabies from the British Isles.

It is obvious that in attempts to control the spread of infectious diseases the cooperation of the population is essential to any success no matter how many inspectors and investigators are at work. Concealment of the early cases of some epidemic disease may cost a community many lives. Frequently disregard by officialdom of warnings is due to stupidity, to a failure to understand what it's all about or to setting up a special lay theory of disease as is so frequently done in denying the existence of such a disease as rabies. City fathers to avoid injury to business had enforced secrecy when plague appeared in one of our cities during the latest epidemic. Manzoni in *Promessi Sposi* tells us that in 1630 the city fathers in Milan tried to conceal the existence of the plague with dire results. In spite of the measures taken in highly civilized countries to interfere with the existence of parasites in our environment and their movement towards susceptible hosts no infectious disease has yet been completely wiped out. In times of stress

and privation endemic diseases gain ground, as did tuberculosis during the World War. For humanity by and large the problem of how to check the multiplication of parasites which have entered the body is still the most pressing as long as the great majority prefer cure to prevention. Here we enter the domain of medical practice. It cooperates in the establishment of hospitals for the care and treatment of individuals afflicted with tuberculosis, leprosy, syphilis, smallpox, and the contagious diseases of childhood, which tend to concentrate and confine infectious material where it can be controlled to the best advantage of the community and the patients. Many highly virulent strains of the different infectious agents are destroyed within the walls of the hospital where dissemination is definitely checked. Medical practice has furthermore gained greatly by the establishment of new concepts of disease itself, which are the direct outcome of the experimental study of disease.

The old idea of a cure in the sense that a disease can be driven out, as it were, by a certain drug or combination of drugs has gradually given way to another point of view. The care and treatment of the patient is directed chiefly towards preventing the disease from taking the next step, from either spreading or augmenting its poisonous action in the body. Treatment when not reenforced by specifics such as antitoxins, quinine, and salvarsan, which definitely check the infectious agent, must rely on the reserve capacities of the body and efforts are directed to support and facilitate these capacities as far as they are understood. Prevention is thus not only of value in anticipating and warding off disease but also in warding off untimely effects of the disease itself. Diphtheria antitoxin acts in meeting toxins newly formed rather than in neutralizing the effects of toxins already bound to the tissues. Hence the importance of early administration. Like a load

slipping down an inclined plane, every advance in certain diseases requires an increasing force to meet and hold it. The best medical practice is thus preventive in theory replacing the old conception of a cure through drugs. The latter view is on a par with belief in miracles. The elimination from the lay mind of the word cure in its crude sense of sidestepping natural processes of defense and recovery when once accomplished will go far in dooming the drug habit and the indiscriminate use of proprietary mixtures of drugs.

The spectacular developments in preventive medicine which have kept at bay most formidable plagues of man and wholly eliminated from certain territories destructive diseases of domestic animals are not without consequences in other fields of human activities but it will require one or several generations to bring them to the surface. As stated in the opening chapter, the human race will have to pay a certain price for these immunities. Moreover, the methods used for achieving the results indicated cannot be dropped but must be frequently overhauled and renovated; otherwise we may be inviting again the spectres exorcised. The public health machinery must be kept in action in certain directions and ready for action in others. The cost represents nature's levy on our desires for security from disease. This levy is continuous and in certain directions growing larger. It will require sacrifices in other fields to meet it and all the ingenuity that can be brought into action to keep human society from moving backwards. Great disasters like the World War have shown how quickly ground is lost when energies are spent in activities indirectly augmenting indigenous plagues like tuberculosis and unwittingly stimulating and spreading others like influenza. In the suppression of disease, as in other human endeavors, there are frequently two roads that to all appearances lead to the same ultimate goal. These in many instances

diverge at a considerable angle. It is the generations that follow us that will decide whether we have chosen the most direct road or whether they must suffer retreat and try another. The choice frequently depends on whether we are looking for an immediate or a more remote gain. In other words it depends on our vision.

INDEX